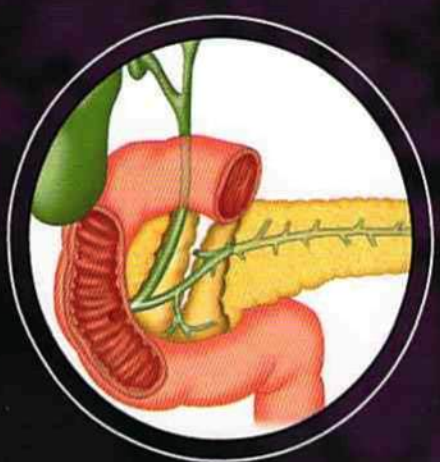
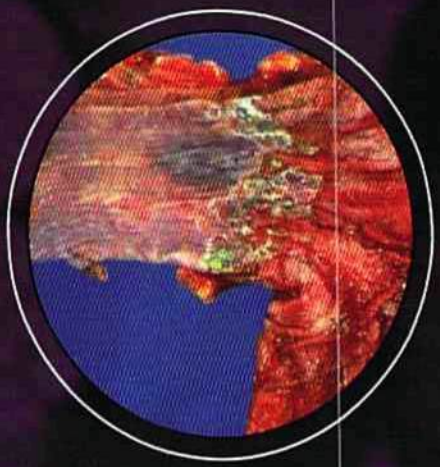
FIRST AID FOR THE® BASIC SCIENCES

Organ Systems





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DEDICATION

To the contributors to this and future editions, who took time to share their knowledge, insight, and humor for the benefit of students.

and

To our families, friends, and loved ones, who supported us in the task of assembling this guide.

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Preface

With this first edition of *First Aid for the Basic Sciences: Organ Systems*, we continue our commitment to providing students with the most useful and up-to-date preparation guides for the USMLE Step 1. Both this text and its companion, *First Aid for the Basic Sciences: General Principals*, are designed to fill the need for a high-quality, in-depth, conceptually driven study guide for Step 1 of the USMLE. They are designed to be used either alone, or in conjunction with the original *First Aid for the USMLE Step 1*. In this way, students can tailor their own studying experience, calling on either book, according to their mastery of each subject.

These books would not have been possible without the help of the hundreds of students and faculty members who contributed their feedback and suggestions. We invite students and faculty to please share their thoughts and ideas to help us improve *First Aid for the Basic Sciences: Organ Systems*. (See How to Contribute, p. xiii.)

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To continue to produce a high-yield review source for the USMLE Step 1, you are invited to submit any suggestions or corrections. We also offer paid internships in medical education and publishing ranging from three months to one year (see below for details). Please send us your suggestions for:

- New facts, mnemonics, diagrams, and illustrations.
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- Corrections and other suggestions.

For each entry incorporated into the next edition, you will receive a $10 gift certificate, as well as personal acknowledgment in the next edition. Diagrams, tables, partial entries, updates, corrections, and study hints are also appreciated, and significant contributions will be compensated at the discretion of the authors. Also let us know about material in this edition that you feel is low yield and should be deleted.

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Embryology

DEVELOPMENT OF THE HEART

Embryonic Heart Structures and Adult Derivatives

The primitive heart tube is formed by the lateral folding and fusion of the endocardial heart tubes. It forms dilatations that will become the structures of the adult heart (see Table 1-1).

Formation of Septa

Atrial Septum

The atrial septum is responsible for the initial division of the primitive atrium into the left and right atria. The steps of development are as follows (see Figure 1-1):

- The **septum primum** begins to move toward the atrioventricular (AV) septum. The space between the leading edge of the septum primum and the AV septum is termed the **ostium primum**. The ostium primum is obliterated when the septum primum reaches the AV septum.
- The **ostium secundum** is formed as tissue regresses in the center of the septum primum.
- The **septum secundum** forms alongside the right edge of the septum primum. It then fuses with the remaining portion of the septum primum to cover the ostium secundum. This fusion forms the **atrial septum**.
- A defect remains in the septum secundum even after fusion to form the atrial septum. This defect is the **foramen ovale**, which allows blood to be shunted from the right atrium (RA) to the left atrium (LA) during fetal life. After birth, the increase in pressure in the LA closes the foramen ovale.

Atrial septal defect (ASD) is an opening in the atrial septum allowing blood to flow between the atria (see Figure 1-2). The most common form is the **ostium secundum** type due to excessive resorption of the septum primum or inadequate formation of the septum secundum. Patients are typically asymptomatic until adulthood, but the clinical course depends on the size of the defect.

TABLE 1-1. Embryonic Heart Structures and Adult Derivatives

Embryonic Structure	Adult Structure
Truncus arteriosus	Ascending aorta and pulmonary trunk
Bulbus cordis	Smooth parts of left and right ventricle
Primitive ventricle	Trabeculated parts of left and right ventricle
Primitive atrium	Trabeculated parts of left and right atria
Left horn of sinus venosus (SV)	Coronary sinus
Right horn of SV	Smooth part of right atrium
Right common cardinal vein and right anterior cardinal vein	Superior vena cava

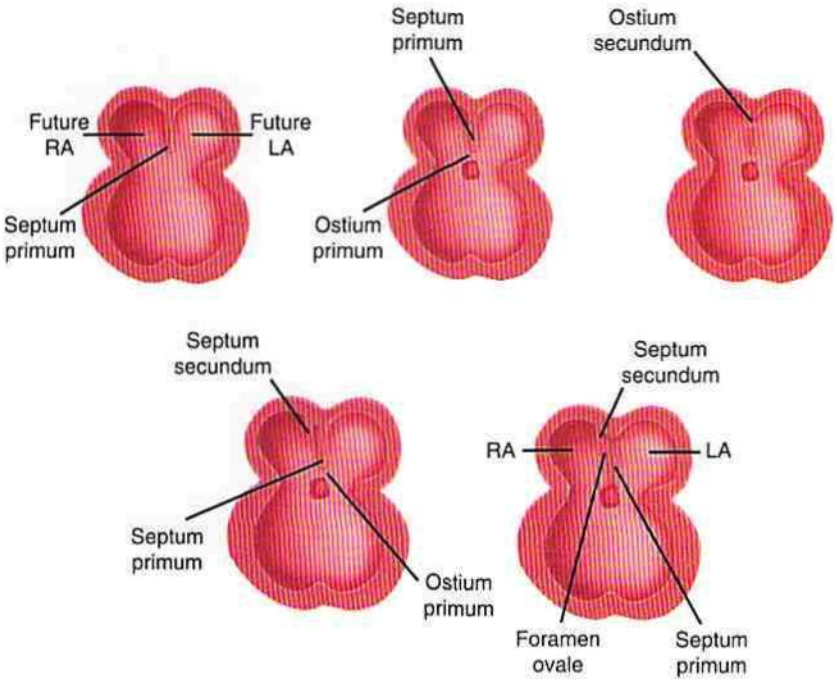


FIGURE 1-1. Embryologic development of the septum.

Classic signs of ASD include the following:

- Wide, fixed splitting of S2
- Systolic ejection murmur heard best in the second intercostal space along the left sternal border

Interventricular Septum

The interventricular septum consists of two parts: the **muscular** portion and the **membranous** portion.

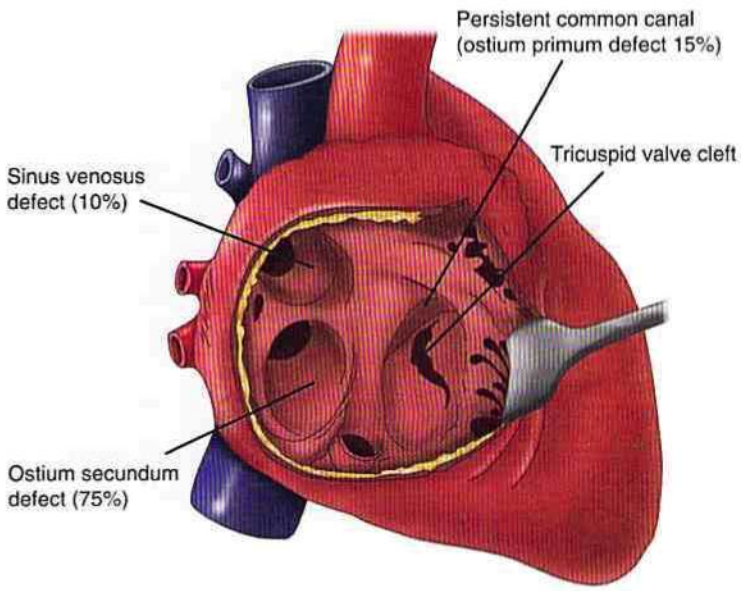


FIGURE 1-2. Various forms of atrial septal defects viewed through the lateral wall of the right atrium.

- The **muscular** interventricular **septum** forms as an upward expansion of the base of the primitive ventricle. It extends toward the AV septum but does not reach it; the resulting gap is the interventricular foramen.
- The **membranous** interventricular **septum** grows downward from the AV cushions and fuses with the muscular interventricular septum, obliterating the interventricular foramen.

Ventricular septal defect (VSD), an abnormal opening in the interventricular septum, is the most common congenital heart malformation (see Figure 1-3). The most common location is in the membranous interventricular septum, resulting from incomplete fusion of the AV cushions in the conotruncal region. Clinical manifestations of VSD are variable depending on the size of the defect. Most are small and resolve spontaneously. Larger VSDs result in left-to-right shunting of blood.

- A classic symptom is **easy fatigability**.
- Cardiac auscultation reveals a **harsh holosystolic murmur** heard best at the left lower sternal border.

KEY FACT

Neural crest cells are also important in craniofacial development. Therefore, many newborns with abnormal migration of neural crest cells will have concurrent facial and cardiac defects.

Aortopulmonary Septum (AP)

The **aorticopulmonary (AP) septum** is derived from **neural crest cells** that migrate into the conotruncal ridges. It is responsible for **separating the truncus arteriosus** into the aorta and pulmonary trunk. As the septum descends, it **spirals** so that the aorta becomes the left ventricular outflow tract and the pulmonary trunk becomes the right ventricular outflow tract. Failure of spiraling leads to congenital malformations.

CLINICAL CORRELATION

Variations of abnormal migration of neural crest cells lead to right-to-left shunts and early cyanosis.

- **Persistent truncus arteriosus** results from abnormal migration of neural crest cells and subsequent **failure of formation of the AP septum**. Therefore, separation of the left ventricular and right ventricular outflow tracts never occurs. The aorta and pulmonary trunk form a common tract leaving the ventricles, which allows mixing of oxygenated and deoxygenated blood. This congenital malformation leads to **right-to-left shunting** of blood and **early cyanosis** in the newborn period.
- **Transposition of the great vessels** occurs with **failure of spiral development of the AP septum**. The left ventricle (LV) is connected to the pul-

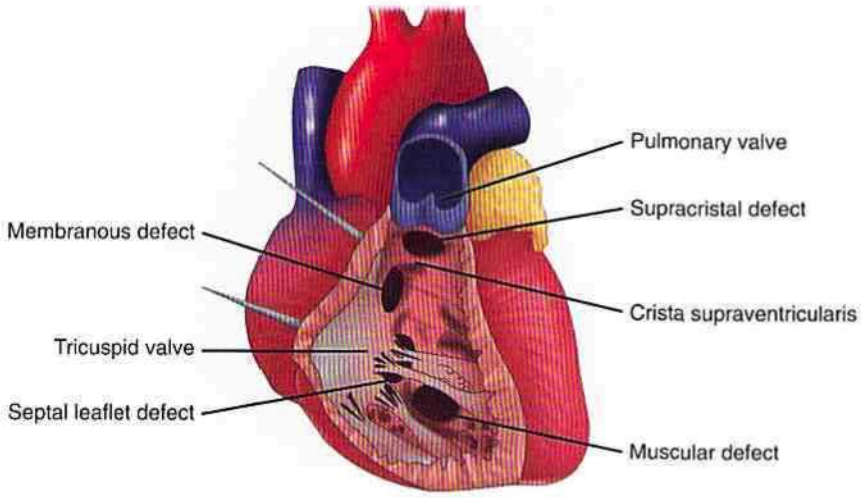


FIGURE 1-3. Ventricular septal defects. Notice the inferiorly located muscular defect and the more superior membranous defect.

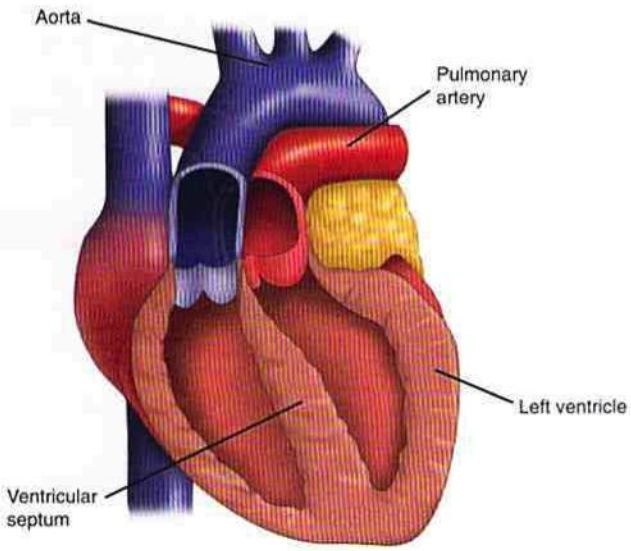


FIGURE 1-4. Transposition of the great vessels.

monary trunk, and the right ventricle (RV) is connected to the aorta (see Figure 1-4). This condition results in a complete **right-to-left shunt** and **early cyanosis**.

- **Tetralogy of Fallot** is caused by **anterior displacement of the AP septum**.
  - The four abnormalities are overriding aorta, pulmonic stenosis, RV hypertrophy, and VSD (see Figure 1-5).
  - The primary defect is termed an "**overriding aorta,**" because the misplaced aorta partially obstructs the right ventricular outflow tract, leading to **right ventricular outflow obstruction (pulmonic stenosis)**. Pul-

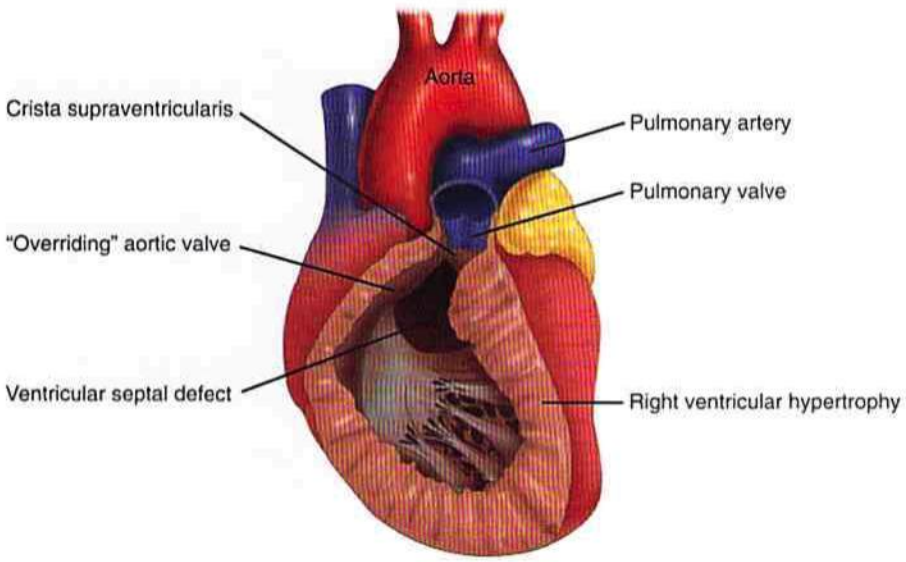


FIGURE 1-5. Tetralogy of Fallot viewed through the RV.

MNEMONIC

Tetralogy of Fallot: PROVe

- **P**ulmonic stenosis
- **RV** hypertrophy
- **O**verriding aorta
- **V**SD

monic stenosis leads to increased pressures in the RV and subsequent **right ventricular hypertrophy**. The **membranous VSD** results from a failure of fusion between the AP septum and the muscular portion of the intraventricular septum (IVS). **Right-to-left shunting** results in **early cyanosis**.

FETAL ERYTHROPOIESIS

Organ Involvement

Fetal erythrocytes are produced in different locations throughout the life of the fetus.

MNEMONIC

Young **L**iver **S**ynthesizes **B**lood.

- Yolk sac (3–8 weeks) during organogenesis
- Liver (6–30 weeks)
- Spleen (9–28 weeks)
- Bone marrow (28 weeks–adult)

Hemoglobin

Fetal hemoglobin consists of two alpha subunits and two gamma subunits (α_2 and γ_2).

FETAL CIRCULATION

Deoxygenated blood leaves the fetus via the **umbilical arteries**. The umbilical arteries travel through the umbilical cord toward the placenta. **Oxygenated blood** (approximately 80% saturated with O_2) returns from the placenta toward the fetus via the **umbilical vein** (see Figure 1-6). Blood from the umbilical vein **bypasses the liver** by flowing through the **ductus venosus** and empties into the inferior vena cava (IVC). The IVC brings blood into the right atrium. Since this blood is already oxygenated, the pulmonary circulation is unnecessary and can be bypassed. Pressures in the right heart are greater than pressures in the left heart in the fetus due to high resistance in the pulmonary circulation. The pressure gradient drives right-to-left shunts, allowing the bypass of the pulmonary circulation. Blood in the RA has **two methods** of bypassing the pulmonary circulation:

- **Flowing through the foramen ovale** to the LA, continuing to the LV, aorta, and eventually supplying the head
- Continuing into the RV, out the pulmonary trunk, and then **through the ductus arteriosus** to the aorta, primarily supplying the trunk and lower extremities

FLASH FORWARD

Indomethacin, a nonsteroidal anti-inflammatory drug (NSAID), is used to close a patent ductus arteriosus (PDA). Exogenous administration of prostaglandins is used to keep a PDA open.

The aorta sends blood to fetal tissues. Deoxygenated blood leaves the iliac arteries via the umbilical arteries to return to the placenta.

After birth, as the neonate begins to breathe, the pulmonary arterial resistance decreases. For the first time, pressures in the left heart exceed pressures in the right heart. The increase in left atrial pressure forces the septum primum against the septum secundum, closing the foramen ovale. Closure of the ductus arteriosus is mediated by **falling levels of prostaglandins** subsequent to increased O_2 content in the circulation.

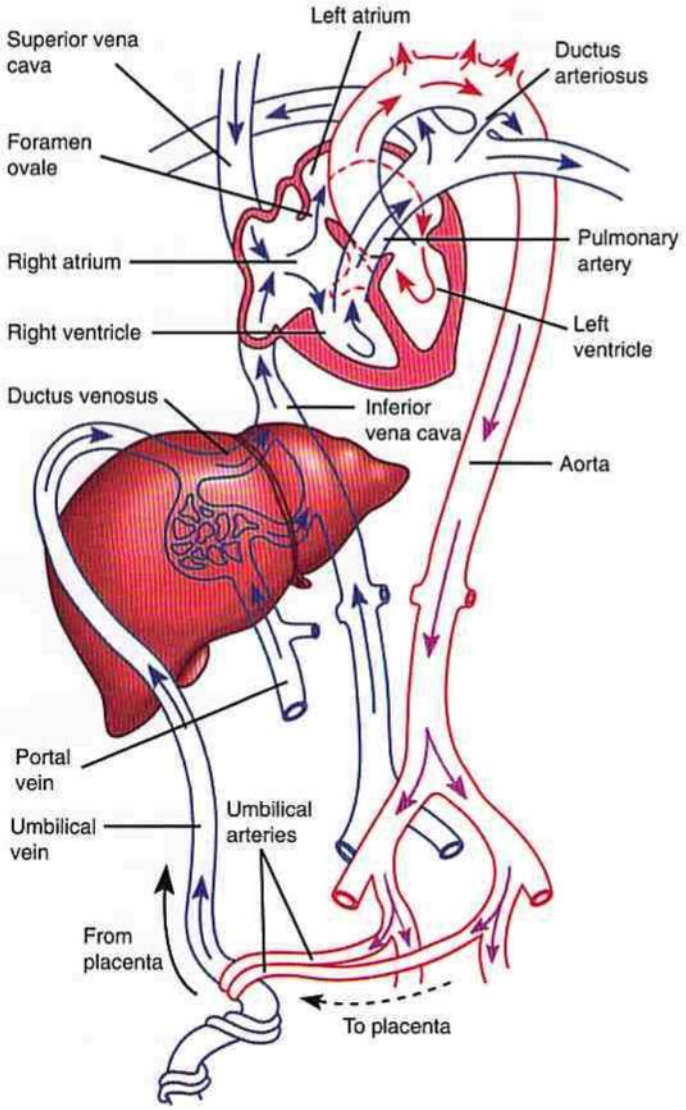


FIGURE 1-6. Fetal circulation. (Modified, with permission, from Ganong WF, *Review of Medical Physiology*, 22nd ed, New York: McGraw-Hill, 2005: 628.)

FETAL-POSTNATAL DERIVATIVES

Some important fetal structures and their postnatal counterparts are highlighted below:

- Umbilical vein → ligamentum teres hepatis
- Umbilical arteries → medial umbilical ligaments
- Ductus venosus → ligamentum venosum
- Ductus arteriosus → ligamentum arteriosus

TABLE 1-2. Aortic Arches and Adult Derivatives

Aortic Arch	Adult Structure
First	Part of maxillary artery
Second	Stapedial artery
Third	Common carotid and proximal internal carotid artery
Fourth	Aortic arch and proximal part of the right subclavian artery
Fifth	Regresses in humans
Sixth	Proximal pulmonary arteries and ductus arteriosus

AORTIC ARCH DERIVATIVES

Table 1-2 shows the adult structures arising from each of the aortic arches.

DEFECTS IN THE ARTERIAL SYSTEM

Coarctation of the Aorta

This is an abnormal narrowing of the aorta in the area surrounding the ductus arteriosus. There are two types: **Preductal** and **postductal**.

- **Preductal coarctation** is constriction of the aorta proximal to the ductus arteriosus. In this type, the ductus arteriosus typically remains patent, resulting in a right-to-left shunt with sufficient blood supply to the lower extremities.
- **Postductal coarctation** is constriction of the aorta distal to the ductus arteriosus (see Figure 1-7). It is characterized by elevated BP in the arms, decreased BP in the legs, and weak or absent femoral pulses. Collateral circulation develops to route blood to the lower extremities. Blood flows from the proximal aorta to the legs via the subclavian artery to the internal thoracic artery, then the intercostal artery, the superior epigastric artery, the inferior epigastric artery, and the external iliac artery. The increased blood flow to the intercostal arteries causes them to dilate and eventually erode into the ribs. This process results in the characteristic **"rib notching"** associated with coarctation of the aorta.

Patent Ductus Arteriosus

Patent ductus arteriosus (PDA) is the failure of the ductus arteriosus to close. A connection persists between the left pulmonary artery and the aortic arch. Since the left heart has higher pressures than the right heart, a **left-to-right shunt** develops, with blood flowing from the aorta into the pulmonary artery. It is most common in premature infants and does not result in early cyanosis. Administration of prostaglandin inhibitors (e.g., indomethacin, NSAIDs) enhances closure of the PDA.

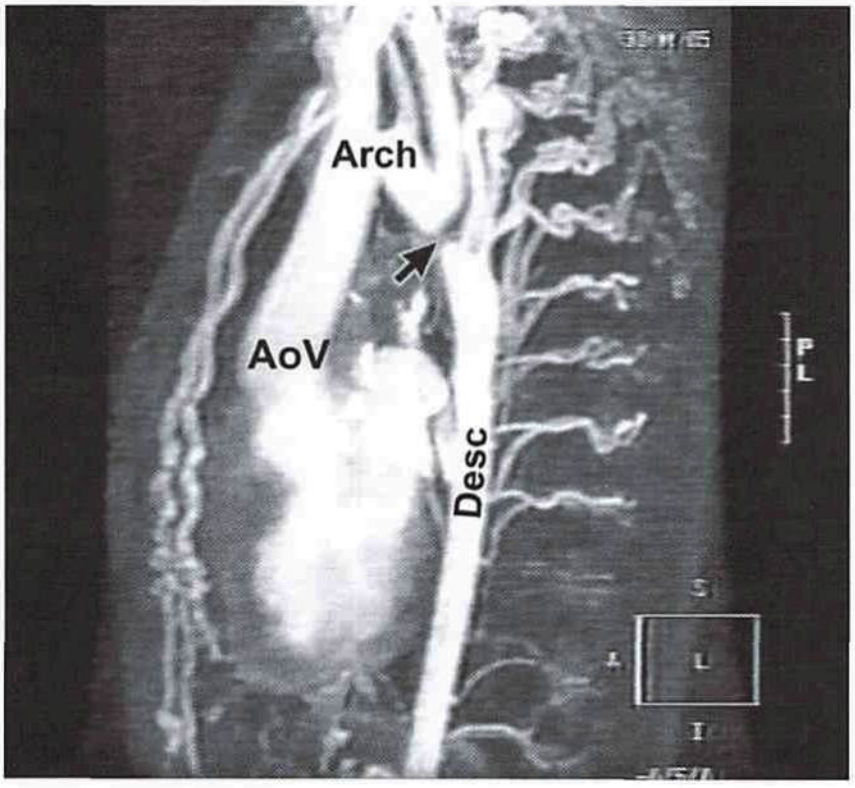


FIGURE 1-7. Postductal coarctation of the aorta. Notice the narrowing of the aorta and the dilated, tortous internal thoracic and intercostal arteries. AoV = aortic valve; Arch = aortic arch; Desc = descending aorta. (Reproduced, with permission, from Fuster V, et al, *Hurst's the Heart*, 11th ed, New York: McGraw-Hill, 2006: 84.)

RIGHT-TO-LEFT SHUNTS: EARLY CYANOSIS

The 5 Ts:

1. Truncus arteriosus
2. Transposition of the great vessels
3. Tetralogy of Fallot
4. Total anomalous pulmonary venous return
5. Tricuspid atresia

These cardiac malformations each results in **shunting of deoxygenated blood** from the pulmonary circulation (or right heart) **into oxygenated blood** in the systemic circulation (or left heart). The addition of deoxygenated blood to oxygenated blood decreases the partial pressure of O_2 in the systemic circulation and causes **early cyanosis**.

LEFT-TO-RIGHT SHUNTS: LATE CYANOSIS

- VSD
- ASD
- PDA

If these defects do not close and high flow continues through the pulmonary circulation, the pulmonary arterial system becomes hypertrophic and even fibrotic. **Pulmonary hypertension** and subsequent **right ventricular hypertrophy** result. When the right heart pressures become higher than the left heart

TABLE 1-3. Disorders and Associated Cardiac Defects

Disorder	Cardiac Defect
22q11 Deletions	Truncus arteriosus, tetralogy of Fallot
Down's syndrome	VSD, ASD
Turner's syndrome	Coarctation of the aorta
Offspring of a diabetic mother	Transposition of the great vessels

KEY FACT

Right-to-left shunts cause early cyanosis.
Left-to-right shunts cause late cyanosis.

pressures, the shunt reverses and becomes right to left. This shunt reversal is termed **Eisenmenger's syndrome** and causes **late cyanosis**. Right-to-left shunts cause cyanosis because deoxygenated blood mixes with oxygenated blood.

CONGENITAL CARDIAC DEFECT ASSOCIATIONS

Certain disorders are associated with particular congenital cardiac malformations (see Table 1-3).

KEY FACT

Enlargement of the LA, a characteristic finding in mitral valve (MV) insufficiency, may cause dysphagia.

KEY FACT

In cardiomegaly the apex is shifted laterally, therefore the point of maximal impulse (PMI) will be palpated more lateral than the midclavicular line.

CLINICAL CORRELATION

Q: An 18-year-old male is stabbed with a knife just to the right of the sternum between the fourth and fifth ribs. Which cardiac structure is penetrated by the knife?
A: The right atrium.

Anatomy

SURFACES AND BORDERS OF THE HEART

- The **anterior (sternal) surface** is formed by the RV (see Figure 1-8).
- The **posterior surface** is formed by the LA and is in close proximity to the esophagus.
- The **right border** is formed by the right atrium.
- The **left border** is formed by the LA and LV.
- The **apex** is formed by the LV.

RELATIONSHIPS OF THE HEART AND GREAT VESSELS

- The **right border** is located between the third and sixth ribs along the right sternal border.
- The **left border** is located between the third and sixth ribs between the midclavicular line and left sternal border.
- The apex is located at the fifth intercostal space, midclavicular line. The point of maximal impulse (PMI) is normally palpated here.
- The **aortic arch** is located at the level of the sternal notch, corresponding to vertebral level T2.
- The **superior vena cava (SVC)** enters the RA at the level of the third rib.

LAYERS OF THE HEART

The heart is composed of three layers: **endocardium**, **myocardium**, and **pericardium**.

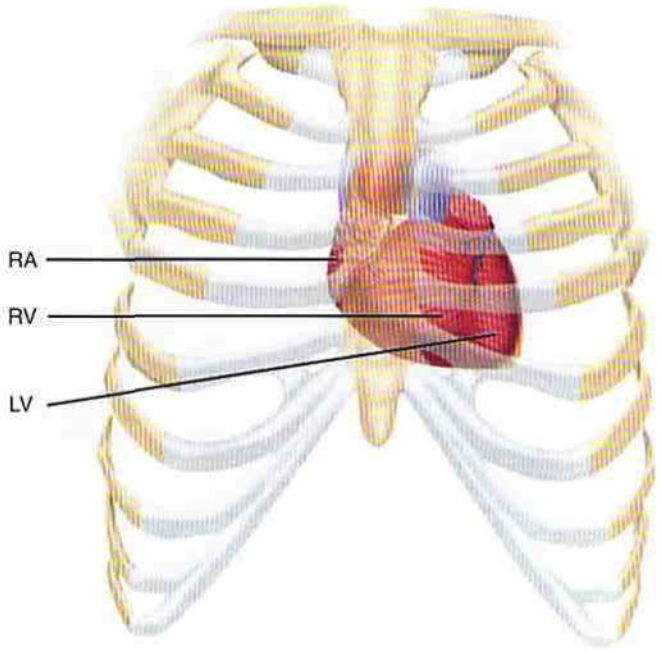


FIGURE 1-8. Anatomic relationships of the heart. RA = right atrium; LA = left atrium; RV = right ventricle.

Endocardium

The endocardium is the innermost layer and contacts the blood in the heart chambers. It is composed of simple squamous epithelium (endothelium) and underlying connective tissue.

Myocardium

The myocardium is the middle layer composed of myocytes, the contractile cells responsible for pumping blood through the heart.

Pericardium

The pericardium is composed of two layers, the outer **fibrous pericardium** and the inner **serous pericardium**. It covers the heart and proximal portion of the great vessels.

- **Fibrous pericardium** is the tough connective tissue that tethers the heart in place via its connections to the sternum anteriorly and the central tendon of the diaphragm inferiorly.
- **Serous pericardium** comprises two layers, the parietal layer and the visceral layer.
  - The parietal layer is continuous with the internal aspect of the fibrous pericardium.
  - The visceral layer, also known as the **epicardium**, is the thin outermost layer of the heart. This layer contains the major branches of the coronary arteries.

CLINICAL CORRELATION

Cardiac tamponade is the compression of the heart by fluid (i.e., blood) in the pericardial sac, leading to decreased cardiac output (CO). Classic signs include decreased mean arterial pressure (MAP), distended neck veins due to inability of the SVC to drain, pulsus paradoxus, and an ECG showing electrical alternans. Treatment is pericardiocentesis.

CLINICAL CORRELATION

Pericarditis is inflammation of the pericardium with various etiologies such as systemic lupus erythematosus (SLE), rheumatoid arthritis, myocardial infarction (MI), TB, and malignancy. Findings include chest pain and friction rub on auscultation, and the ECG shows diffuse ST elevations in all leads.

CORONARY ARTERY ANATOMY

Major Branches

The coronary arteries arise from the proximal portion of the aorta (the aorta's first branches) as the **right coronary artery (RCA)** and the **left coronary artery**

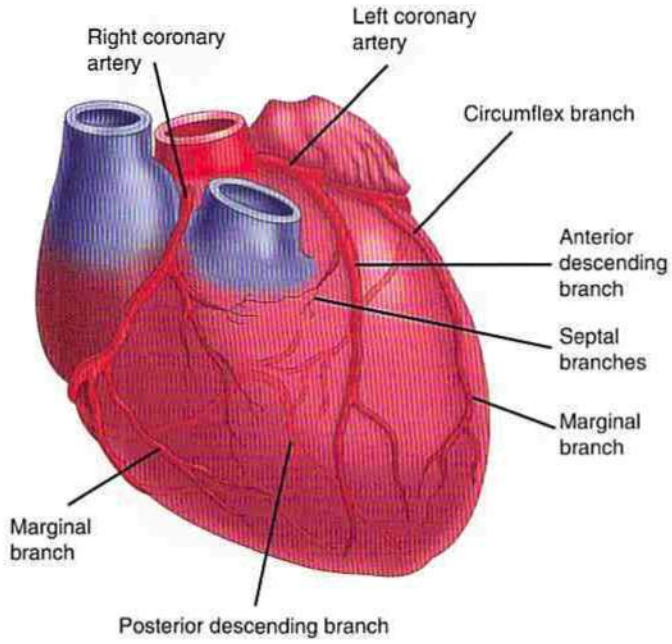


FIGURE 1-9. Coronary artery circulation.

CLINICAL CORRELATION

Subendocardial infarctions result from repeated episodes of temporary occlusion of a coronary artery (e.g., unstable angina) or from severe anemia or hypotension. ECG findings show ST-segment depression. Histologic findings include fibrosis and vacuolization of the subendocardial area.

KEY FACT

Tachycardia shortens diastole so the heart receives less blood supply.

(LCA) (see Figure 1-9). These vessels lie just deep to the epicardium on the surface of the heart.

The heart receives a dual blood supply: The **epicardium** and **myocardium** are supplied by the **coronary arteries** and their branches, while the **endocardium** receives O_2 and nutrients from direct contact with blood inside the heart chambers.

When flow through a coronary artery is compromised, the subendocardial tissue is most vulnerable to ischemic injury because it lies in the zone farthest from either blood supply.

Flow through the coronary arteries occurs mainly during diastole. The contraction of the myocardium during systole increases external pressure on the vessels and inhibits blood flow through them.

Major branches of the LCA are the left anterior descending artery (LAD) and left circumflex artery.

TABLE 1-4. Arterial Supply of the Heart in Right-Dominant Coronary Circulation

LAD	Left Circumflex	RCA
Apex	Lateral wall of LV	Lateral wall of RV
Anterior wall of LV	Posterior wall of LV (20%)	Posterior wall of LV (80%)
Anterior two-thirds of IV septum	Posterior one-third of IV septum (20%)	Posterior one-third of IV septum (80%) SA node AV node

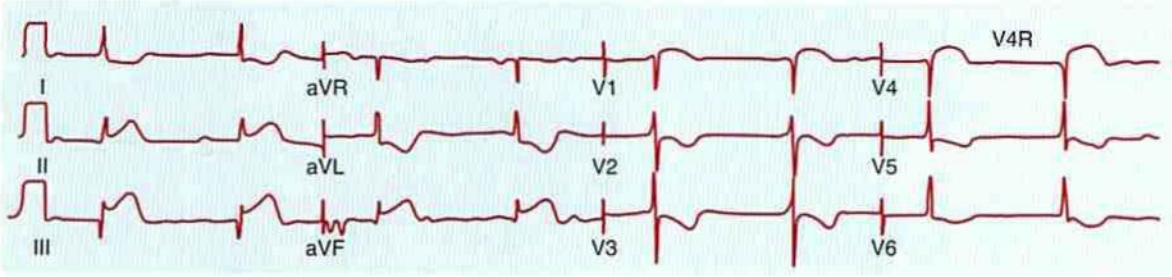


FIGURE 1-10. ECG findings in AMI of the RV. (Modified, with permission, from Fuster V, et al, *Hurst's the Heart*, 11th ed, New York: McGraw-Hill, 2006: 300.)

Major branches of the RCA are the **marginal artery** and the **posterior descending artery**.

Dominant Circulation

Table 1-4 summarizes the arterial supply of the heart. This **right dominant coronary circulation** occurs in 80% of the population.

Myocardial Infarctions

The coronary artery **most commonly occluded** (40%–50%) is the **LAD**, resulting in infarction of the anterior portion of the ventricles, the cardiac apex, and/or the IVS. The RCA is the second most commonly occluded, followed by the left circumflex.

CLINICAL CORRELATION

Acute MI of the inferior portion of the heart (RV) is associated with characteristic ECG findings of ST-segment elevation in leads II, III, and aVF (see Figure 1-10 and Table 1-5).

CONDUCTION SYSTEM

The cardiac conduction system is responsible for distributing electrical impulses throughout the heart so that the atria and ventricles function in concert as an effective pump (see Figure 1-11).

Sinoatrial Node

- The **sinoatrial (SA) node** is the **cardiac pacemaker**, setting the rate at approximately 70 bpm.
  - The SA node contains specialized myocytes that depolarize rhythmically and serve to initiate the spread of electrical impulses throughout the heart.
  - It is located at the junction of the RA and SVC just beneath the pericardium and is supplied by the **SA nodal artery**, typically a branch of the RCA.

TABLE 1-5. ECG Findings with MI

Area of Infarct	Coronary Artery Involved	Leads with ST Elevation
Inferior wall (RV)	RCA	II, III, aVF
Septum	LAD	V_2, V_3
Lateral wall (LV)	Left circumflex	I, aVL, V_5, V_6

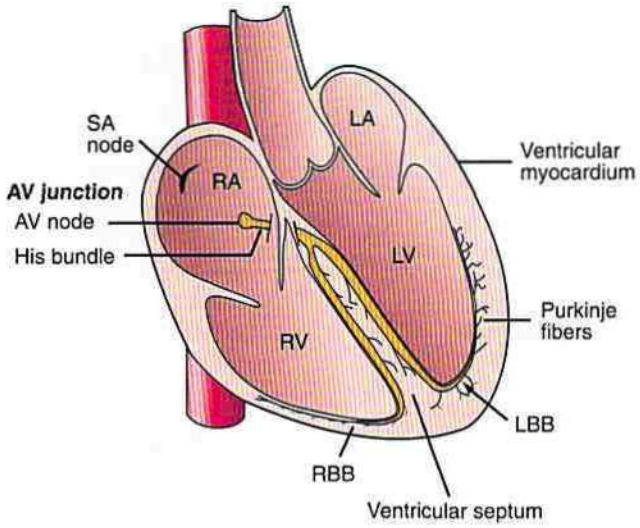


FIGURE 1-11. Anatomy of the conduction system in the heart. To initiate a contraction, the SA node fires at an intrinsic rate of 100–120 bpm. The impulse travels through the atrial myocardium and arrives at the AV node, located at the base of the right atrium. The impulse stalls at the AV node. The slowed conduction through the AV node allows time for the atria to depolarize fully and completely empty their contents into the ventricles, before the ventricles themselves are driven to contract. The AV nodal delay is key for efficient systolic pumping. If the SA node is diseased or fails to fire, the AV node initiates the heart contractions at rate of 40–60 bpm. From the AV node, the impulse propagates through the His bundle along the interventricular septum, into bifurcating paths called the right bundle branch (RBB) and left bundle branch (LBB). These bundles subdivide into Purkinje fibers that relay the impulse to the ventricular myocardium. The Purkinje fibers conduct the most quickly, to enable a rapid and synchronized ventricular contraction. (Modified, with permission, from Kasper DL, Braunwald E, Fauci AS, et al, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 1311.)

KEY FACT

The SA node receives input from both the sympathetic nervous system (accelerating its rate of depolarization) and the parasympathetic nervous system via the vagus nerve (slowing its rate).

- From the SA node, the impulses disperse across the atrial septum to the LA and toward the AV septum of the right heart. The impulse eventually reaches the **AV node**.

AV Node

- The **AV node** is located in the subendocardial connective tissue in the interatrial septum near the ostium of the coronary sinus.
  - It receives blood supply from the **AV nodal artery**, also a branch of the RCA.
  - The AV node is responsible for dispersing the electrical signal to both ventricles, which it accomplishes via the AV bundles (**bundles of His**).

CLINICAL CORRELATION

Damage to the AV node (most often caused by ischemia) may result in complete heart block. Impulses are unable to get from the RA to the RV; thus, ventricular rate is slowed and cardiac output is low. Treatment is usually a permanent pacemaker.

Bundles of His

- The **bundles of His** travel parallel to the IVS deep to the endocardium, eventually terminating as the **Purkinje fibers** in the walls of both ventricles.

TABLE 1-6. Characteristics of Heart Valves

Valve	Location	Structure	Site of Auscultation	Phase When Valve Is Open
Aortic	Between LV and aorta	Semilunar (3 cusps)	Left second intercostal space (IS) at the sternal border (SB)	Systole
Pulmonic	Between RV and pulmonary trunk	Semilunar (3 cusps)	Right second IS at the SB	Systole
Mitral	Between LA and LV	Bicuspid	Left fifth IS at the midclavicular line	Diastole
Tricuspid	Between RA and RV	Tricuspid	Left fifth IS at the SB	Diastole

HEART VALVES AND SITES OF AUSCULTATION

The four heart valves are the **aortic, pulmonic, mitral, and tricuspid valves** (see Table 1-6). It is important to understand how valve movement relates to the cardiac cycle.

Many cardiac diseases and valvular lesions result in abnormal heart sounds (see Figure 1-12). Heart sounds are due to blood flow; therefore, the site of auscultation of a particular valve is downstream to the direction of flow through that valve.

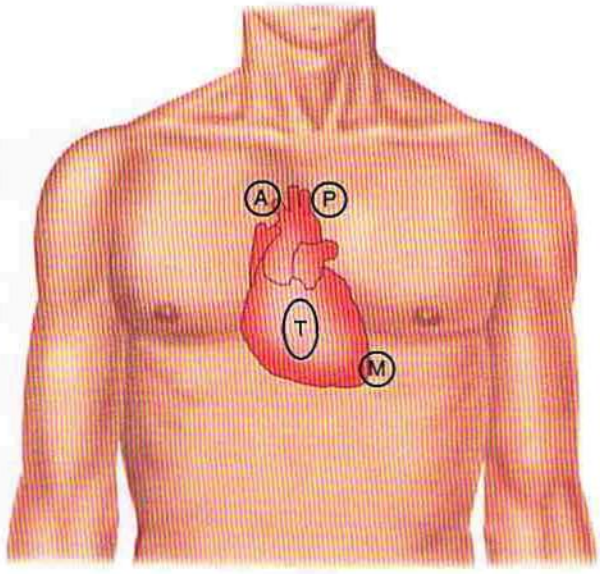


FIGURE 1-12. Sites of cardiac auscultation. A = aortic valve; P = pulmonic valve; T = tricuspid valve; M = mitral valve.

MNEMONIC

All–**A**ortic
Patients–**P**ulmonic
Take–**T**ricuspid
Meds–**M**itral

CLINICAL CORRELATION

Aortic stenosis (AS) causes a crescendo-decrescendo systolic ejection murmur. The murmur is best heard at the left second intercostal space and typically radiates toward the carotid arteries and/or the cardiac apex.

CLINICAL CORRELATION

Mitral regurgitation (MR) causes a holosystolic blowing murmur heard best at the cardiac apex. It can sometimes be confused with tricuspid regurgitation; however, the murmur of tricuspid regurgitation becomes louder with inspiration.

TABLE 1-7. Location and Anatomic Relationships of Major Branches of the Aorta

Vertebral Level	Artery	Nearby Structures	Arterial Branches	Major Structures Supplied
T12	Celiac trunk	Posterior to the gastrohepatic ligament; superior to curvature of stomach	Common hepatic, splenic, left gastric artery	Foregut structures (liver, gallbladder, stomach, spleen, beginning of duodenum)
L1	Superior mesenteric	Posterior to neck of pancreas and stomach antrum	Middle colic, right colic, ileocolic artery	Midgut structures (lower duodenum to splenic flexure of colon, including appendix)
L2	Renal	Posterior to renal veins	Segmental artery (gives rise to interlobar, arcuate, interlobular arteries), inferior suprarenal artery	Kidneys, part of suprarenal glands
L3	Inferior mesenteric	Posterior to third part of duodenum	Left colic, sigmoid, superior rectal artery	Hindgut structures (splenic flexure of colon to proximal rectum)
L4	Common iliacs (aortic bifurcation)	Anterior to formation of IVC	External/internal iliac artery	Pelvis, lower extremities

MAJOR BRANCHES OF THE AORTA

Table 1-7 shows the location of major branches of the aorta, their nearby structures, and the structures that they supply.

Physiology

The cardiovascular (CV) system, which can be modeled as a pump (heart) and a set of tubes (blood vessels), distributes O_2, nutrients, and other substances to the tissues while removing metabolic by-products from the tissues.

CARDIAC ELECTROPHYSIOLOGY

Cardiac nodal cells and myocytes are excitable cells that generate characteristic action potentials. Nodal cells share similar qualities with excitable cells such as neurons in that both rely on cationic Na^+ inflow to reach the threshold membrane potential to fire action potentials. However, a key difference is that nodal action potentials are triggered **automatically** by spontaneous depolarization.

Myocytes resemble the skeletal myocyte in that both rely on Ca^{2+} inflow for contraction, but key differences include the action potential's shape (plateau in atrial and ventricular myocytes due to inward Ca^{2+} current) and electrical coupling via gap junctions.

Resting Membrane Potential

The membrane potential (V_m) in all cells is determined by:

- **Relative permeability of certain ions** (e.g., K^+, Na^+, Ca^{2+}) determines which ion's equilibrium potential predominates. The membrane potential at any point in the action potential is determined by the relative contribution of different ion conductances. The predominant ion conductance pushes the membrane potential toward that ion's equilibrium/Nernst potential. For example, at rest, the myocyte is more permeable to K^+, and thus the membrane potential is closer to the Nernst potential of K^+ than to that of Na^+.
- **Relative intracellular and extracellular concentrations of these ions.**

The resting membrane potential is determined primarily by the potassium (K^+) conductance, $[K^+]_{intracellular}$ ($[K^+]_i$), and $[K^+]_{extracellular}$ ($[K^+]_e$). Since $[K^+]_i >> [K^+]_e$, K^+ diffuses out of the cell and down its concentration gradient, causing the V_m to become more negative (losing positive charge to the outside). At a certain membrane potential, the net force driving potassium ions down its electrochemical gradient equals the net concentration gradient driving ions across the membrane. This potential at which there is no net movement of ions across the membrane is the **equilibrium (or Nernst) potential** and can be calculated:

$$V_m = 61.5 \log \left(\frac{[K^+]_e}{[K^+]_i} \right) mV$$

In contrast, since Na^+ concentration is higher in the extracellular space, Na^+ tends to enter the cell and make the membrane potential more positive. The Na^+-K^+-ATPase pump maintains the ionic gradient across the cell membrane by pumping 3 Na^+ out for every 2 K^+ pumped in. This sets up an Na^+ gradient such that $[Na^+]_e$ is greater than $[Na^+]_i$ (see Figure 1-13).

Cardiac Action Potentials

The heart has two populations of excitable cells: one produces a fast response action potential and one produces a slow response action potential (see Figure 1-14). Fast-response action potentials occur in the atrial and ventricular myocytes and Purkinje fibers, whereas slow response action potentials occur in the SA and AV nodes. These action potentials differ in their shape and conduction velocity (see Tables 1-8 and 1-9).

Slow Response Action Potential: SA Node

Intrinsic pacemaker of the heart with the highest intrinsic rate of firing, determined by the slope of phase 4 depolarization. In contrast, the AV node and His-Purkinje systems are latent pacemakers; they take over as pacemaker cells

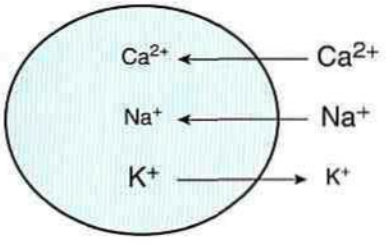


FIGURE 1-13. Relative intracellular and extracellular concentrations of Ca^{2+}, Na^+, and K^+.

KEY FACT

Remember that $[K^+]_i >> [K^+]_e$ and $[Na^+]_e >> [Na^+]_i$ (i = intracellular fluid, e = extracellular fluid).

KEY FACT

Inward current → positive charge (e.g., K^+, Na^+) enters cell → depolarizes V_m (makes less negative).
Outward current → positive charge leaves cell → hyperpolarizes V_m (makes more negative).

KEY FACT

The most important difference between fast- and slow-response cardiac action potentials is the ion responsible for the phase 0 upstroke:
Fast response action potential = fast inward Na^+ current.
Slow response action potential = slow inward Ca^{2+} current.

FLASH FORWARD

The four classes of antiarrhythmic drugs target specific channels/receptors:
Class I: Na^+ channel blockers
Class II: β-Blockers
Class III: K^+ channel blockers
Class IV: Ca^{2+} channel blockers

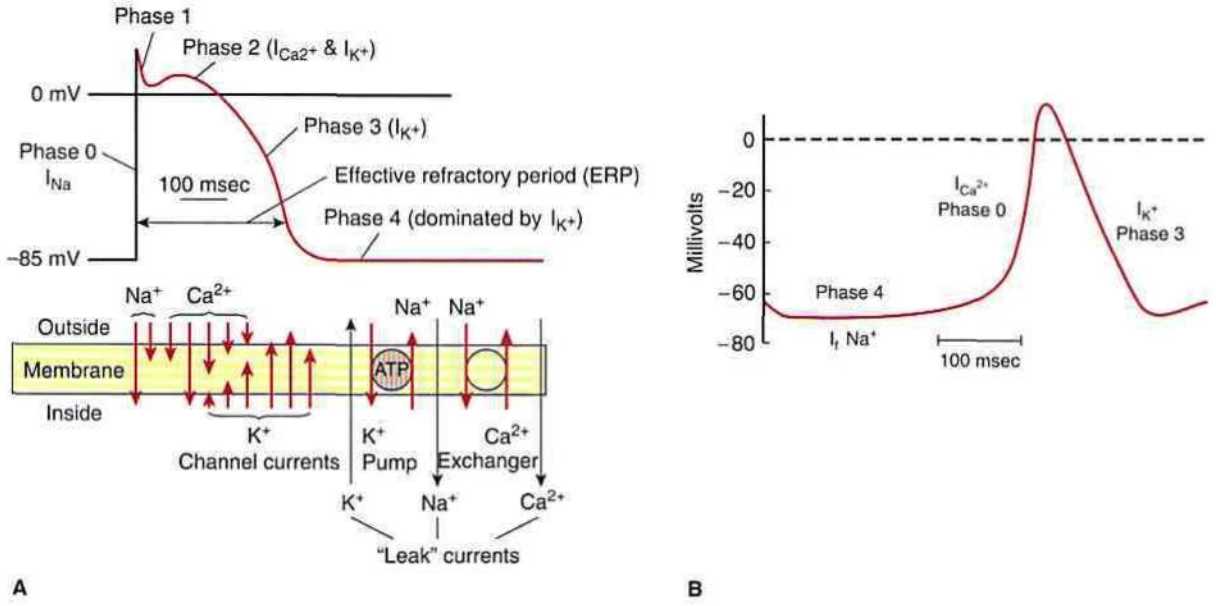


FIGURE 1-14. Fast response (A) and slow response (B) cardiac action potentials. (Modified, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005.)

KEY FACT

Overdrive suppression: Because the SA node fires the fastest, at a rate of 100–120/min, it by default sets the heart rate (HR) unless diseased (i.e., RCA infarct). In that situation, the AV node fires at 40–60/min, and the Purkinje system comes in last at 30–40/min.

if the SA node is suppressed. The primary, secondary, and tertiary pacemaker cells are related to their rates of phase 4 depolarization: SA node > AV node > His-Purkinje.

Conduction Velocity

Depends on the size of the inward current during the action potential upstroke (i.e., phase 0); a larger inward current corresponds to a faster conduction velocity. It is fastest in the Purkinje system and slowest in AV node. A slower conduction velocity in the AV node means that the excitation of the ventricles is delayed. The AV nodal delay enables the atria to empty fully into the ventricles prior to depolarization of the ventricles, such that there is more time for ventricular filling and greater cardiac output in a given beat.

TABLE 1-8. Comparison of Slow and Fast AP

	Slow Pacemaker AP	Fast AP
Length of AP	150 ms (SA, atria), 250–300 ms (AV, ventricular)	100 ms
Tissues involved	SA and AV nodes	Atria, ventricles, Purkinje fibers
Phases	0 G_{Ca2+} III I_{K+} IV I_f	0. Increased G_{Na+} I. Decreased G_{Na+} II. Increased G_{Ca2+} III. Increased I_{K+}, decreased I_{Ca2+}
Targeting antiarrhythmics	Class II β-blockers (phase IV), class IV Ca channel blockers (phase 0)	Class Ia, Ib, Ic (phase 0), class III (phase III)

TABLE 1-9. Phases of Fast- Versus Slow-Response APs

	Fast-Response (Ventricular) AP	Slow-Response (Pacemaker) AP
Upstroke: Phase 0	Atrial and ventricular myocytes, Purkinje fibers. Due to rapid inward **Na^+** current through voltage-gated Na^+ channels	SA, AV nodes Due to slow inward **Ca^{2+}** current through voltage-gated Ca^{2+} channels; lack fast voltage-gated Na^+ channels, which results in a slow conduction velocity
Initial repolarization: Phase I	Inactivation of voltage-gated Na^+ channels; voltage-gated K^+ channels begin to open.	Not present
Plateau: Phase II	Ca^{2+} influx through voltage-gated Ca^{2+} channels balances K^+ efflux; Ca^{2+} influx also triggers release of intracellular Ca^{2+} from sarcoplasmic reticulum and myocyte contraction	Not present
Repolarization: Phase III	Massive K^+ efflux due to opening of voltage-gated slow K^+ channels and closure of voltage-gated Ca^{2+} channels	Increased K^+ conductance causes K^+ efflux
Phase IV	Resting potential; high K^+ permeability through K^+ channels	Slow diastolic depolarization; membrane potential spontaneously depolarizes as Na^+ conductance increases; accounts for automaticity of SA and AV nodes; the slope of phase IV in the SA node determines heart rate
Conduction velocity	0.3–3.0 m/s	0.01–0.10 m/s

Refractory Period

The period of the action potential in which cardiac cells cannot be excited; it can be defined in three ways (see Figure 1-15).

- **Absolute:** Begins at phase 0 and ends after phase 2 (plateau); reflects time in which no action potential can be generated, regardless of the amount of inward current delivered
- **Effective:** Period in which a **conducted** action potential cannot be generated; slightly longer than the absolute refractory period
- **Relative:** Period in which an action potential can be generated with a larger-than-usual amount of inward current

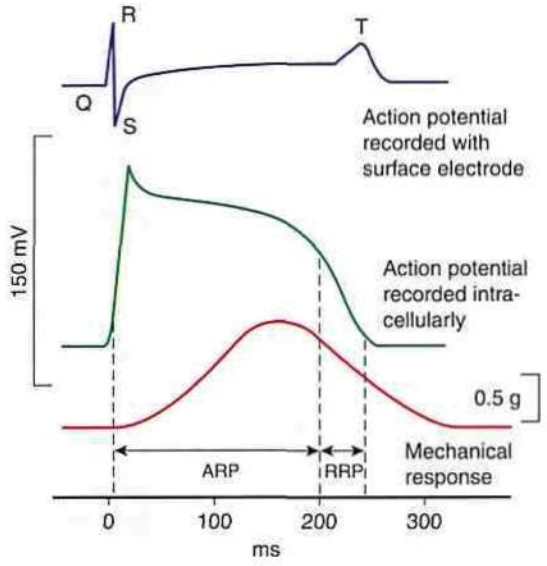


FIGURE 1-15. Absolute (ARP), effective (ERP), and relative (RRP) refractory periods in the ventricle. The refractory period sets the rate of firing, and consequently, the heart rate. Longer refractory periods lead to slower heart rates. (Modified, with permission, from Ganong WF, *Review of Medical Physiology*, 22nd ed, New York: McGraw-Hill, 2005: 80.)

CARDIAC MUSCLE AND CONTRACTION

When the cardiac action potential reaches the axon terminal, depolarization of the terminal opens voltage-gated Ca^{2+} channels causing neurotransmitter (acetylcholine [ACh]) vesicle fusion and exocytosis. ACh binds to the postsynaptic receptor, causing depolarization of the postsynaptic muscle cell. Through the process of excitation-contraction coupling, the depolarization event triggers the release of intracellular Ca^{2+} from the sarcoplasmic reticulum (SR). Increased intracellular Ca^{2+} binds troponin C and changes the conformation of the myosin-actin complex, ultimately leading to contraction.

Excitation-Contraction Coupling

Coupling depends on several structures in the myocardial cell that coordinate the contraction response to the cardiac action potential.

- **Sarcomere.** Contractile unit of myocardial cell that runs from Z line to Z line (see Figure 1-16). Composed of thick filaments (myosin) and thin filaments (actin, troponin, tropomyosin).
- **T tubules.** Parts of the cell membrane that invaginate at the Z lines. They carry action potentials into the cell interior.
- **Sarcoplasmic reticulum.** Intracellular site of storage and release of Ca^{2+}, which is used in excitation-contraction coupling.
- **Intercalated disks.** Located at the ends of cells. Mediate adhesion between cells.
- **Gap junctions.** Occur at the intercalated disks. Provide a path of low resistance for action potentials to rapidly spread between cells.

Myocardial Contraction and Relaxation

These features allow the cardiac myocyte to translate the electrical signal (action potential) into a physical response (contraction) through the following steps: Extracellular Ca^{2+} enters myocardial cell → Ca^{2+} induces intracellular Ca^{2+} release → myocardial contraction, and finally myocardial relaxation.

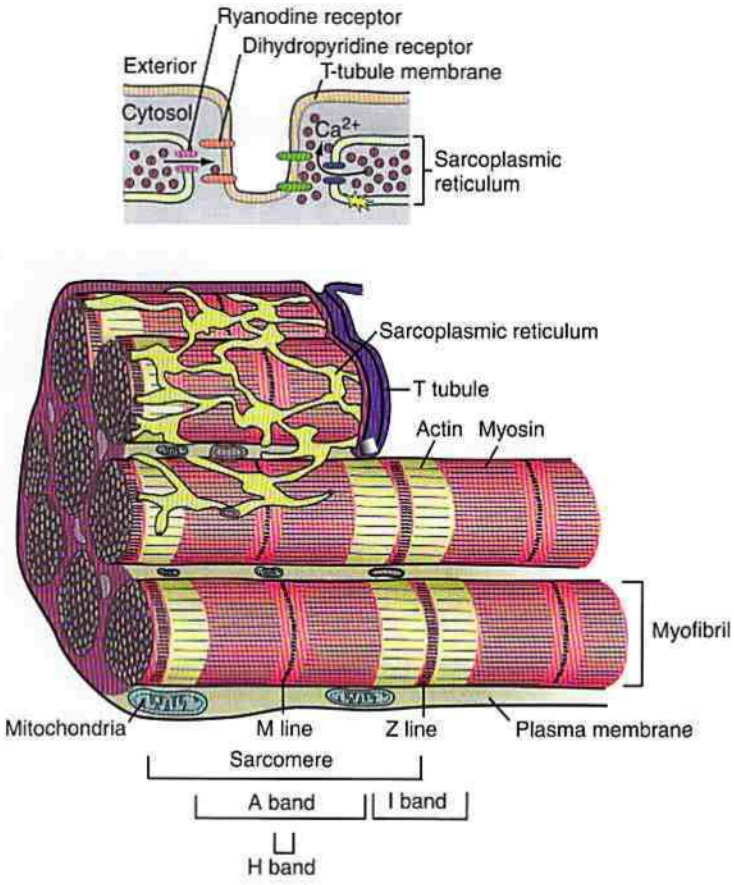


FIGURE 1-16. Schematic of cardiac myocyte.

- **Influx of extracellular Ca^{2+} into myocardial cells.** Action potential spreads from cell membrane into the T tubules. During the plateau (phase 2) of the action potential, extracellular Ca^{2+} enters the cell through voltage-gated Ca^{2+} (L-type Ca^{2+}) channels.
- **Ca^{2+}-induced Ca^{2+} release.** The influx of extracellular Ca^{2+} is not sufficient to induce muscle contraction. To solve this problem, extracellular Ca^{2+} binds to Ca^{2+} release channels (ryanodine receptors) on the SR, stimulating more Ca^{2+} release from the SR. Amount of Ca^{2+} released from the SR depends on:
  - Size of inward current during plateau of the action potential
  - Amount of Ca^{2+} stored in SR
- **Myocardial contraction.** Ca^{2+} release from the SR increases intracellular $[Ca^{2+}]$. Ca^{2+} binds to troponin C, which causes a conformational change and moves tropomyosin out of the myosin-binding groove on the actin filament. Myosin binds the newly exposed actin. The bound myosin head undergoes a change in shape that moves the thin filament (power stroke) and shortens the sarcomere. Contraction results in HIZ shrinkage—aka H, I, and Z band contraction (see Figure 1-17).
- **Myocardial relaxation.** Occurs when Ca^{2+} is pumped back into the SR via Ca^{2+}-ATPase. This reduces intracellular $[Ca^{2+}]$ and removes Ca^{2+} from troponin.

KEY FACT

The contractility (inotropy) that can be generated by cardiac muscle is related to intracellular $[Ca^{2+}]$.

KEY FACT

During contraction, the H, I, and Z bands shorten. Only the A band stays constant throughout the cycle.

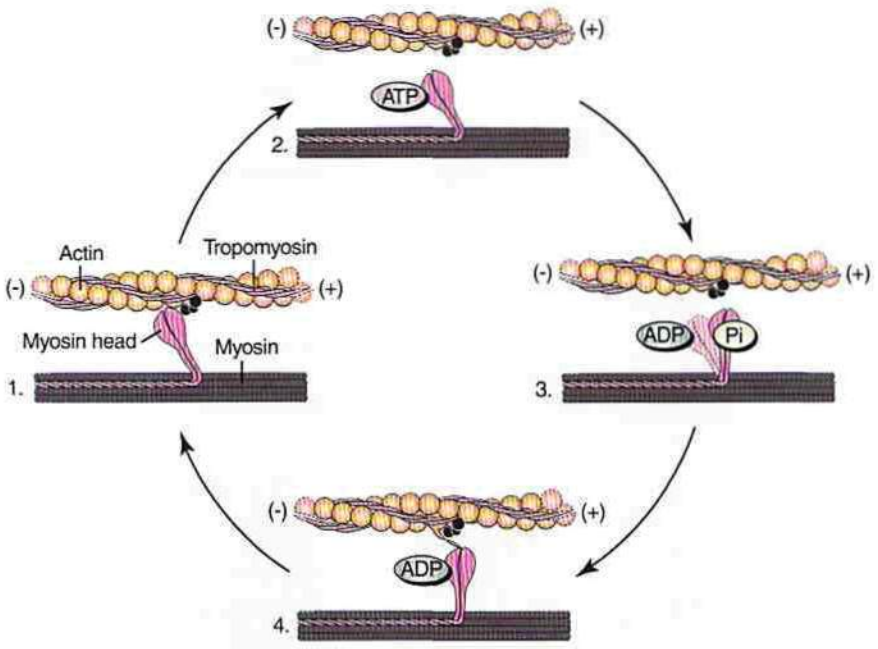


FIGURE 1-17. Skeletal muscle contraction. The process in myocytes is very similar.

Cardiac and skeletal muscles differ physiologically. In contrast to skeletal muscle:

- Cardiac muscle action potential has a plateau, due to Ca^{2+} influx.
- Cardiac nodal cells spontaneously depolarize, resulting in automaticity.
- Cardiac myocytes are electrically coupled to each other by gap junctions.
- Cardiac muscle cells have more mitochondria.
- Cardiac muscle increases contractile force through changes in fiber contractility (compared with increasing the number of skeletal muscle fibers activated).

Thus, cardiac muscle contraction requires a series of coordinated steps. When the action potential opens voltage-gated Ca^{2+} channels, this increases intracellular $[Ca^{2+}]$ and triggers Ca^{2+}-induced Ca^{2+} release from the SR. Ca^{2+} binds troponin C, allows myosin-actin binding, and permits myocardial contraction.

Contractility

Contractility is the amount of force cardiac muscle can generate at a given muscle length, and is related to intracellular $[Ca^{2+}]$. It can be estimated by ejection fraction (EF, normal = 55%). It increases with increased HR, sympathetic stimulation, and cardiac glycosides.

$$EF = \frac{\text{stroke volume}}{\text{end-diastolic volume}} \text{ (normal = 55\%)}$$

Contractility and, by proxy, stroke volume (SV) are increased with:

- **Increased HR.** As HR increases, Ca^{2+} clearance is less efficient during relaxation after contraction, and intracellular Ca^{2+} builds up.
- **Sympathetic stimulation.** Stimulation leads to increased Ca^{2+} influx and also increases the activity of the SR Ca^{2+}-ATPase.
- **Cardiac glycosides (digoxin).**

Conversely, contractility and SV are decreased in the setting of:

- β-Blockade, calcium channel blockers
- Heart failure
- Peripheral nervous system stimulation
- Acidosis, hypoxia, hypercapnia

Length-Tension Relationship in Ventricles

Sarcomere length affects the force of contraction (see Figure 1-18). At the optimal length, there is maximal actin-myosin overlap, which results in the maximum systolic contraction. Sarcomere length is related to **preload**.

Preload

The load seen by cardiac myocytes while the heart is in its relaxed state. It represents the stretch on the filled ventricle during diastole, before contraction takes place. Related to left ventricular end-diastolic volume (LVEDV) and left ventricular end-diastolic pressure (LVEDP). An acute increase in preload in diastole stretches the myocytes and causes optimized overlapping of actin-myosin complexes, leading to increased force of contraction in systole.

Afterload

Load against which the myocytes must contract to generate cardiac output. Represents the force that must be generated to push blood from LV into the aorta. Related to peak LV pressure. An acute increase in afterload reduces the volume of blood that is ejected during systole.

Frank-Starling Relationship

The greater the venous return, the greater the cardiac output. It can be thought of as the length-tension relationship applied to the whole heart: The force of systolic contraction is proportional to the initial length of cardiac muscle in diastole (preload).

- **Molecular/cellular level:** Sarcomere length is proportional to the force of contraction that it can generate: The longer it is, the more cross-bridges that form, and the greater the tension that can develop. The increased stretch that the myocytes see when the ventricle is filled translates into optimized overlapping of the actin-myosin filaments, which generate increasing force of contraction when the cross-bridges recycle. Up to a certain point, the increased stretch/preload leads to greater contractility.

FLASH FORWARD

Cardiac glycosides such as **digitalis** increase the force of contraction by inhibiting Na^+–K^+–ATPase in the myocardial cell membrane. This results in increased intracellular [Na^+] and decreased Na^+ concentration gradient across the cell membrane. Since Ca^{2+} extrusion relies on the Na^+ concentration gradient (Na^+–Ca^{2+} exchange), less Ca^{2+} is removed and intracellular [Ca^{2+}] is increased.

KEY FACT

Preload increases with exercise (slightly), increasing blood volume (overtransfusion), and excitement (sympathetics).

KEY FACT

In the LV, afterload is equivalent to aortic pressure and MAP/systolic pressure.
In the RV, afterload is equivalent to pulmonary artery pressure and LVEDV.

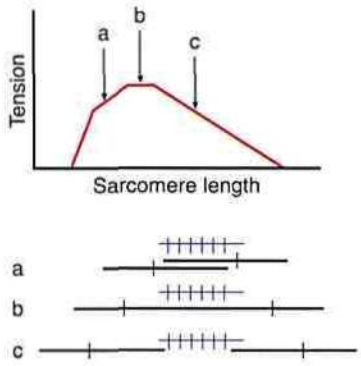


FIGURE 1-18. Effect of sarcomere length on the force of contraction. There is an ideal length that maximizes the overlap between actin and myosin (b) and maximizes contraction. If the sarcomere is too short (a) or too long (c), the myosin and actin do not interact as well.

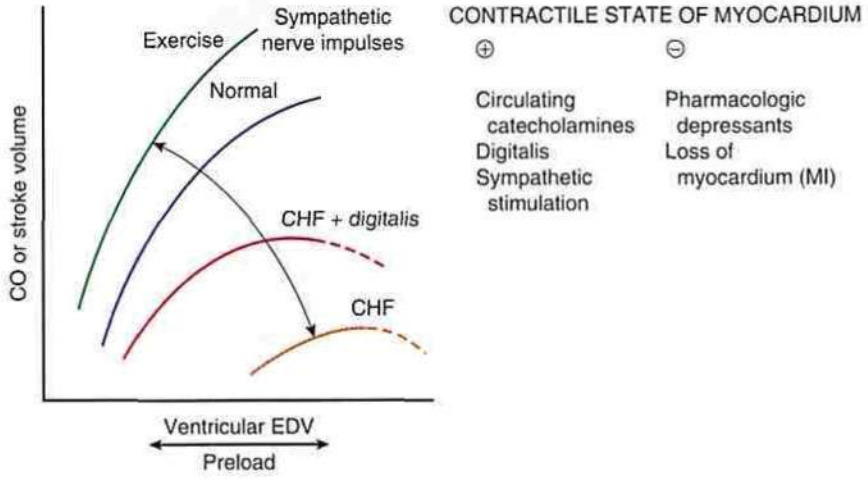


FIGURE 1-19. Frank-Starling curve and the effect of positive and negative inotropic agents.

- **Organ level:** Increased venous return or end-diastolic volume (preload) leads to increased ventricular fiber length and increasing tension, which increases stroke volume and cardiac output. The Frank-Starling curve can be shifted up or down when the heart is in a state of increased or decreased contractility, respectively (see Figure 1-19).
- **Caveat:** This rule holds up to a certain threshold preload. The heart at its strongest and contracting most vigorously can handle only so much venous return before it becomes overstretched. At a preload beyond this threshold value, actin-myosin overlap is no longer optimal, as the cross-bridges cannot form. As a result, contractility decreases as the preload continues to increase. This accounts for the descending limb of the length-tension curve at excessively high preloads.

KEY FACT

Increased venous return → increased cardiac output.

PRESSURE–VOLUME (PV) LOOPS

PV loops describe the relationship between LV volume and pressure during the five phases of the cardiac cycle (see Figure 1-20). The bottom curve,

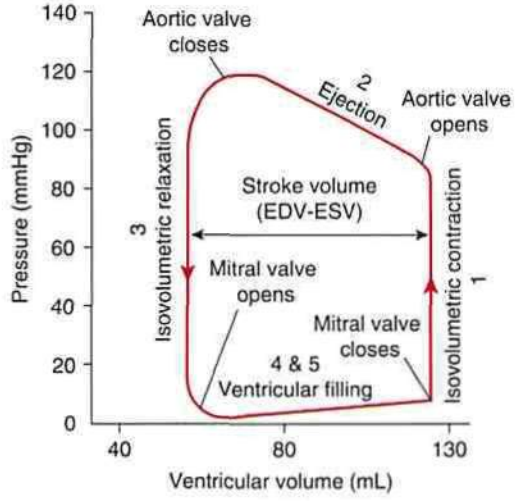


FIGURE 1-20. LVP–volume loop. (Modified, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005.)

TABLE 1-10. Variables that Affect Stroke Volume in the Pressure–Volume Loop

Variable	Effect on Stroke Volume
Increased preload and venous return (e.g., aortic insufficiency)	↑
Increased afterload (e.g., hypertension, aortic stenosis)	↓
Increased contractility (e.g., exercise)	↑

which is the compliance curve, defines how the pressure in the LV changes as it is filled in diastole (LVEDV). The five phases and how they relate to systole and diastole are as follows.

Diastole

MV opens and the ventricle rapidly fills until the pressure of the LV is greater than that of the LA and the **MV closes**. Corresponds to P and PR intervals on ECG.

- **Isovolumetric contraction.** Period between MV closure and aortic valve (AoV) opening. Since the MV and AoV are closed, the LV is a closed chamber and contracts under a constant volume. Eventually, LV pressure is greater than that in the aorta and the AoV opens. Corresponds to the QRS on ECG and is the period of highest O_2 consumption.

Systole

AoV has opened:

- **Systolic ejection.** Period between AoV opening and closing. Volume ejected from the LV in this phase is the **SV** (width of pressure–volume loop). LV pressure decreases and the **AoV closes**. Corresponds to ST on ECG.
- **Isovolumetric relaxation.** Period between AoV closing and MV opening. LV is a closed chamber with both the MV and AoV closed. LV relaxes until pressure in the LV drops to that of the LA, the **MV opens**, and blood moves from the LA to the LV. Corresponds to T wave on the ECG.
- **Rapid filling.** Period just after MV opening.
- **Slow filling.** Period just before MV closure.

SV can be altered with changes in preload, afterload, or contractility (see Table 1-10 and Figure 1-21).

CARDIAC AND VASCULAR FUNCTION CURVES

The cardiac function and vascular function curves plot how cardiac output and venous return change with respect to right atrial pressure or end-diastolic volume (see Figure 1-22). The factors affecting these functions include:

- **Cardiac function curve (Frank-Starling length-tension relationship).** Increased preload/venous return leads to increased cardiac output, and decreased preload leads to decreased cardiac output.
- **Vascular function curve.** Increased right atrial or systemic pressure and/or decreased blood volume decreases venous return to the heart (decreased preload), and vice versa.

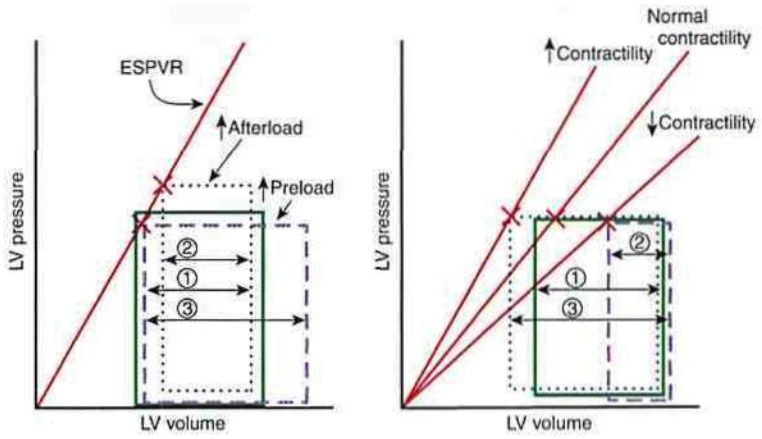


FIGURE 1-21. Effect of changes in preload, afterload, and contractility on SV (width of pressure-volume loop). (Modified, with permission, from Kasper DL, Braunwald E, Fauci AS, et al, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 1363.)

- **Decreased blood volume** (hemorrhage, shock) shifts the vascular function curve left and downward, leading to decreased potential venous return and increased mean systemic pressure through sympathetic stimulation.
- **Exercise** shifts the vascular function curve upward and to the right, in addition to increasing systemic pressure through sympathetic stimulation.

- **X-intercept of the vascular function curve yields mean systemic pressure.** Pressure in the RA when there is no blood flow through the CV system (heart was stopped); pressure is equal throughout the CV system (i.e., there is no pressure gradient).

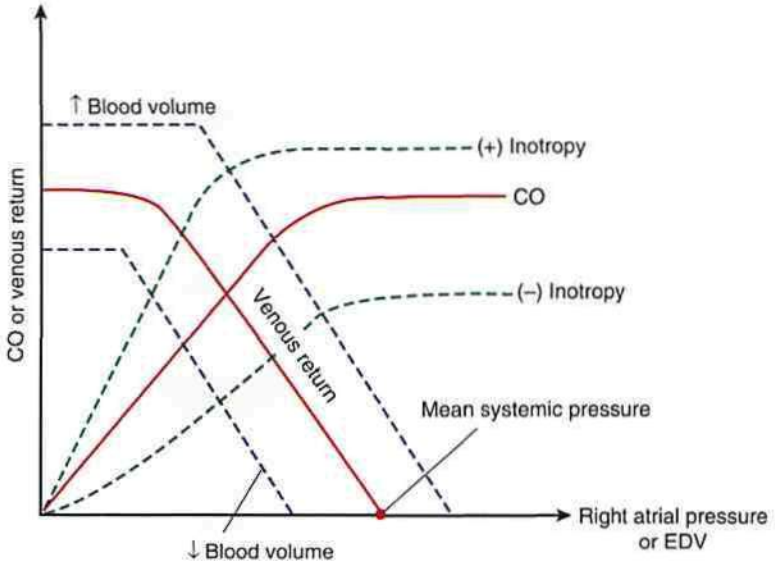


FIGURE 1-22. Cardiac and vascular function curves and dependence on inotropy and blood volume, respectively. Changes in inotropy affect the cardiac function curve. Changes in blood volume affect the venous return curve. Changes in total peripheral resistance (TPR) affect both curves. Increased TPR causes a counterclockwise rotation of the venous return curve and a clockwise rotation of the cardiac output curve.

- **Intersection of cardiac and vascular function curve yields the equilibrium point.** Occurs when cardiac output = venous return. Provides the resting cardiac output.

CARDIAC OUTPUT

The volume of blood pumped per minute from either ventricle, which should be equal in the absence of pathology, is known as cardiac output. Normal resting cardiac output is 4–8 L/min and can increase 5–6 times during exercise. Cardiac output can be calculated using SV and HR (Cardiac output = SV × HR) or measured using Fick's O_2 method.

Fick's Cardiac Output

Cardiac output is indirectly calculated by measuring O_2 consumption. Based on conservation of mass, the amount of O_2 delivered to the body (product of cardiac output and the difference in pulmonary artery and vein $[O_2]$) must equal O_2 consumed.

$$\text{Fick's CO} = \frac{O_2 \text{ consumption}}{([O_2]_{\text{pulmonary vein}} - [O_2]_{\text{pulmonary artery}})}$$

Stroke Volume

SV is the difference between end-diastolic volume and end-systolic volume, or the volume of blood ejected by the LV during a heartbeat. It varies directly as a function of contractility and preload, and varies inversely with afterload. SV increases with increased preload, decreased afterload, or increased contractility. Other variables that affect SV and contractility are summarized in Table 1-11.

Ejection Fraction

EF is the fraction of blood received by the LV (end diastolic volume) that is ejected (SV) and directly reflects state of contractility of heart. A larger percentage of LV blood volume ejected (larger EF) reflects an increased contractile state.

$$EF = \frac{\text{stroke volume}}{\text{end-diastolic volume}} \text{ (normal = 55\%–80\%)}$$

$$SV = \frac{CO}{HR} = EDV - ESV$$

$$EF = \frac{SV}{EDV} \times 100\%$$

TABLE 1-11. Factors Affecting Contractility and Stroke Volume

CONTRACTILITY AND SV ↑ WITH:	CONTRACTILITY AND SV ↓ WITH:
Catecholamines (↑ activity of the Ca^{2+} pump in sarcoplasmic reticulum)	β_1-Blockade
↑ Intracellular Ca^{2+}	Heart failure
↓ Extracellular Na^+	Acidosis
Digitalis (↑ intracellular Na^+, causing ↑ intracellular Ca^{2+})	Hypoxia/hypercapnia

KEY FACT

Mean systemic pressure is increased by:
- Increased blood volume
- Decreased venous compliance (blood shifted from veins to arteries)
- Exercise (sympathetic stimulation)

KEY FACT

Factors that increase O_2 consumption:
- Increased afterload
- Increased contractility
- Increased HR
- Increased size of heart (increases radius → increases tension via LaPlace's Law)

MNEMONIC

SV CAP

Stroke Volume affected by:
Contractility
Afterload
Preload

THE CARDIAC CYCLE

PV loops divide the cycle into five phases: Isovolumetric contraction, systolic ejection, isovolumetric relaxation, rapid filling of the LV, and slow filling of the LV (see Figure 1-20). The heart cycle can be traced from systole through diastole with PV loops (described earlier), pressure tracings in the heart, and heart sounds.

Pressure Tracings during the Cardiac Cycle

Pressure Changes in Diastole and Systole

- **Diastole:** Begins with MV opening and the LA emptying into the LV. As blood fills the LV, pressure in LV (P_{LV}) rises slowly. At the end of diastole, the LA contracts to empty into the LV and the MV closes. The LV contracts, causing a large rise in LV pressure until it exceeds that of aortic pressure (P_{Ao}) and the AoV opens.
- **Systole:** The AoV opens and the LV ejects blood into the aorta. As P_{LV} decreases and ejection rate slows down, the AoV closes when P_{LV} is less than P_{Ao}. LV relaxes under a constant volume and the MV reopens once P_{LV} is less than LA pressure (P_{LA}).

Pressure Changes in Jugular Venous Pulses, LV, and Aorta

- **Jugular venous pulses:** Provides another complementary pressure tracing to follow mechanical (as opposed to valvular) events of systole and diastole; consists of a, c, and v waves, and Y descent (see Figure 1-23).
  - **a** wave: Atrial contraction
  - **c** wave: RV contraction (tricuspid valve bulging into the RA)
  - **v** wave: Increased RA pressure due to filling against closed tricupsid valve
  - **Y** descent: Corresponds to rate of atrial emptying as the tricuspid valve opens
- **LV pressure.** In diastole, during LV filling, P_{LV} equals P_{LA} until the MV closes. During isovolumetric contraction, P_{LV} rises dramatically until it exceeds P_{Ao}, and then the AoV opens to initiate systole. As blood rushes out of the LV, the P_{LV} drops, continuing to decrease as the AoV closes, and continues to drop more as the LV relaxes, until it equals that of the P_{LA}. The MV opens once more and diastole begins again.
- **Aortic pressure.** In diastole, P_{Ao} is greater than P_{LV} and the AoV remains closed. When P_{LV} is equal to or greater than P_{Ao}, the AoV opens and P_{Ao} increases as blood (SV) is moved into the aorta. P_{Ao} begins to decrease as the ejection rate slows down, P_{LV} drops, and the AoV closes to begin diastole.

KEY FACT

Jugular venous distention is seen in right heart failure (RHF).

KEY FACT

The slope of the Y descent decreases in tamponade (i.e., the RA empties slower) and increases in constrictive pericarditis.

Pressures in the various heart chambers are measured with a Swan-Ganz catheter (see Figure 1-24). The pulmonary capillary wedge pressure (PCWP) is a good approximation of LA pressure.

Heart Sounds

The state of valve closure, ventricular filling, or pathology can be extrapolated from four heart sounds (see Table 1-12).

S1 and S2

S1 and S2 are due to valve closures. S1 is due to closure of the mitral and tricuspid valves; S2 is due to closure of the aortic and pulmonic valves. S1 is usually auscultated as a single sound. S2, which is really composed of two

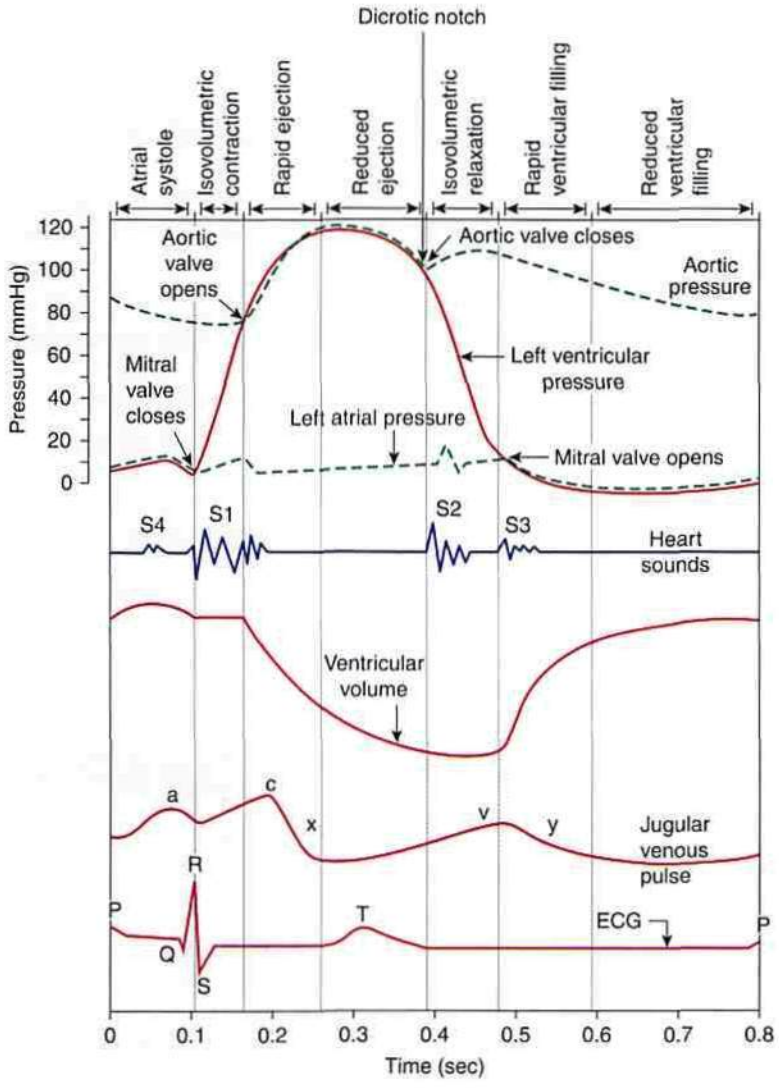


FIGURE 1-23. Mechanical and electrical events of a single cardiac cycle. The seven phases are separated by vertical lines. (Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd. New York: McGraw-Hill, 2005.)

sounds closely linked in time (AoV closure and pulmonic valve closure), splits during inspiration for two reasons:

- Inspiration decreases intrathoracic pressure, which increases venous return to the heart and delays pulmonic valve closure (P2 delayed).

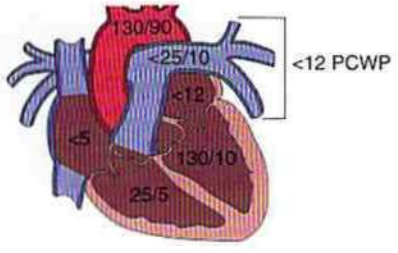


FIGURE 1-24. Normal pressures in the heart in mmHg. SVC = 5; RA = 5–10; RV = 25/5; LA = 25/10; LV = 130/10; Ao = 130/90.

TABLE 1-12. Heart Sounds and Significance

SOUND	SIGNIFICANCE
S1	MV and tricuspid valve closure; the MV closes before the tricuspid, so S1 may be split.
S2	Aortic and pulmonary valve closure; the AoV closes before the pulmonic valve; inspiration causes increased splitting of S2.
S3	At end of rapid ventricular filling; normal in children; in adults, associated with dilated CHF.
S4	Filling of ventricle by atrial systole; not audible in normal adults; its presence suggests high atrial pressure or stiff ventricle.

- Inspiration has the opposite effect on A2 since blood wants to stay in the lung (lower intrathoracic pressure). This transiently decreases venous return to the LA and LV, reduces LV filling, shortens LV emptying, and allows earlier AoV closure (A2) (see Figure 1-25).

REGULATION OF ARTERIAL PRESSURE

Arterial pressure varies in a pulsatile pattern during the cardiac cycle. It is assessed by measuring systolic pressure and diastolic pressure, and using both to calculate pulse pressure and MAP (see Figure 1-26).

- **Systolic pressure.** Highest arterial pressure of the cardiac cycle. Measured after the heart contracts and blood has been ejected into the arterial system. In older patients, it is increased due to age-related stiffening of large arteries. In younger patients, it is increased due to increased SV. Decreases with dehydration, β-blockers, diuretics, and blood loss.
- **Diastolic pressure.** Lowest arterial pressure of the cardiac cycle. Corresponds to the time when the heart is relaxed and blood is returning to the heart via the venous system. Decreases with aortic stiffening (decreased compliance), which results in less blood volume in the aorta at the onset of diastole.

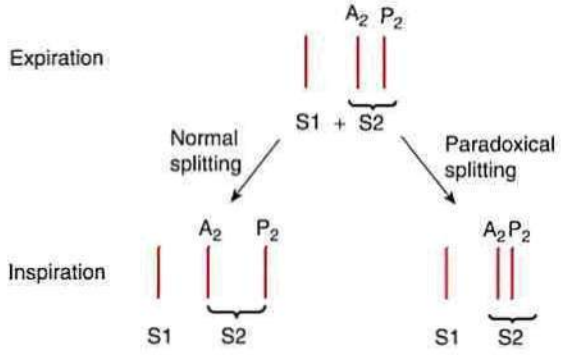


FIGURE 1-25. S2 splitting: Normal and pathologic states. During inspiration, the pulmonic valve closes even later, augmenting the split between A2 (AoV closure) and P2 (pulmonic valve closure). However, in paradoxical splitting—which is associated with aortic stenosis—P2 and A2 come closer during inspiration.

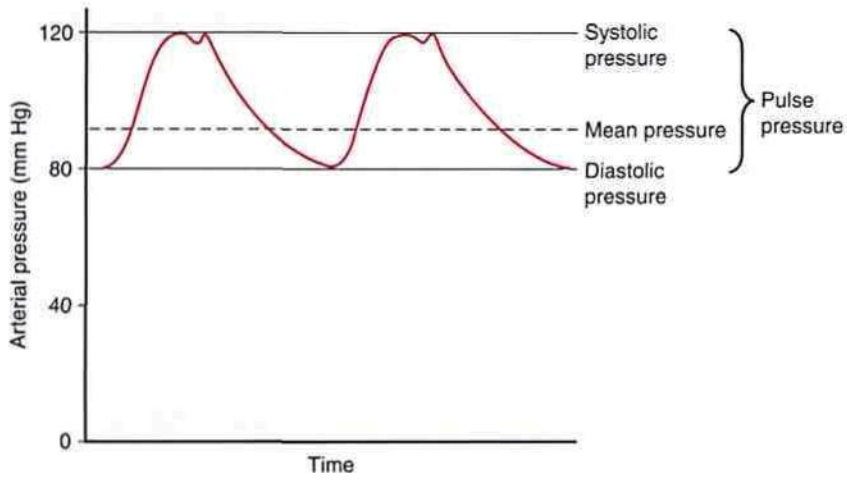


FIGURE 1-26. Arterial pressure during the cardiac cycle.

- **Pulse pressure.** Difference between systolic and diastolic pressure and depends mainly on SV. Decreased vessel capacitance secondary to aging (think stiffer pipes) increases the pulse pressure since systolic pressure increases while diastolic pressure decreases.

$$\text{Pulse pressure} = \text{systolic pressure} - \text{diastolic pressure}$$

- **MAP** = diastolic pressure + $^1/_3 \times$ (pulse pressure)

Regulation of Mean Arterial Pressure

Changes in MAP are detected by either baroreceptors or the kidney as decreased extracellular circulating volume (ECV) (see Figure 1-27). Decreased baroreceptor firing is centrally processed and relayed to the autonomic nervous

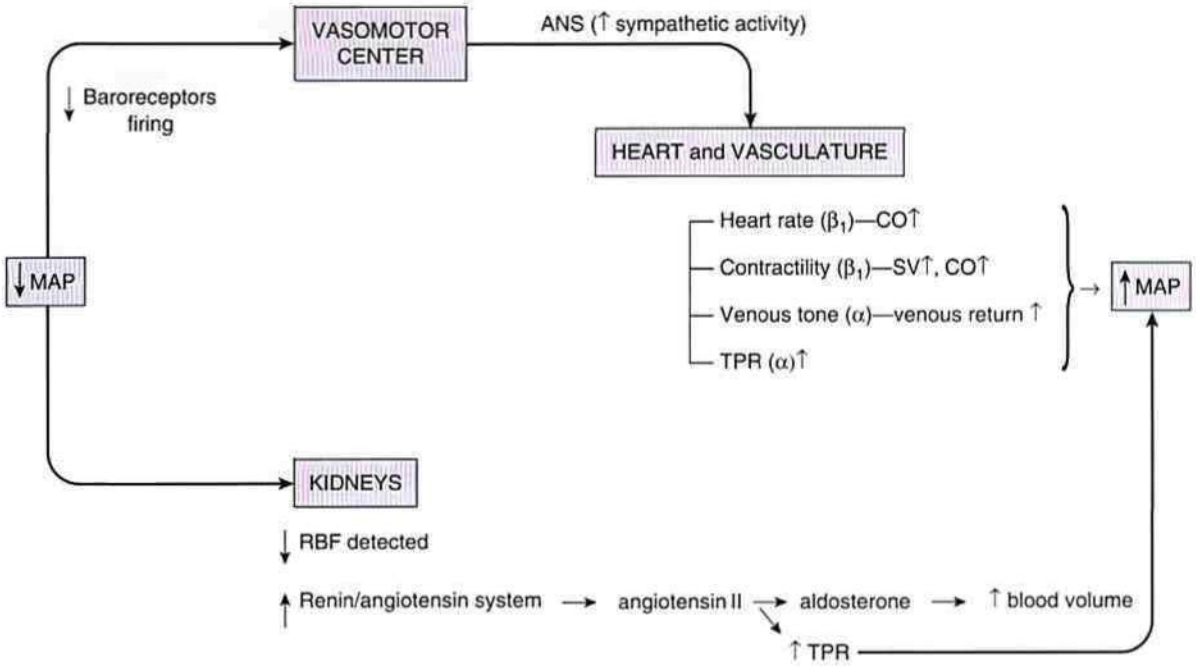


FIGURE 1-27. Control of MAP.

KEY FACT

Mechanisms to regulate BP:
- Baroreceptor reflex (short term): Baroreceptors in the sinus are always active, and increased activity indicates rise in BP
- RAAS (long term)
- Cerebral ischemia leading to hypercapnia
- Hypoxia with $Po_2 < 60$ mmHg
- Severe volume depletion leading to ADH secretion
- Atrial stretch mediated by ANP
- Autoregulation

system (ANS), whereas decreased ECV activates the renin-angiotensin-aldosterone system (RAAS). The baroreceptor reflex is neurally controlled and has a fast (minute-to-minute) response, while the RAAS is hormonally controlled with a slower regulation response.

Mechanisms other than the fast baroreceptor reflex and slower RAAS to regulate arterial pressure are based on Pco_2, Po_2, blood volume, and atrial pressure (see Table 1-13).

Baroreceptor Reflex: Short-Term Regulation of Blood Pressure

Stretch receptors located within the walls of the carotid sinus and aortic arch respond to both MAP and pulse pressure. Carotid sinus baroreceptors are tonically active, so increased activity indicates an increase in BP, and decreased firing indicates decreased arterial pressure. Changes in firing rate at the carotid sinus (transmitted by CN IX) and at the aortic arch (transmitted by CN X) are relayed to the vasomotor center of the brain stem and elicit ANS response.

For example, decreased firing secondary to perceived drop in BP leads to decreased PS and increased sympathetic outflow to the heart, leading to increased HR, contractility, SV, and vasoconstriction of arterioles and veins (see Figure 1-28).

Maneuvers that affect baroreceptor reflex:
- Increased SNS (sympathetic nervous system) output, decreased PNS output (leading to lowered BP): Carotid occlusion, cutting afferents, orthostasis/lying to standing, and fluid loss
- Turning PNS on, turning SNS off (leading to acute rise in BP): Carotid massage, volume loading, and weightlessness

TABLE 1-13. Other Mechanisms that Regulate Arterial Pressure

TRIGGER	RESPONSE
↑ Pco_2 in brain tissue (cerebral ischemia)	↑ Sympathetic outflow to heart and blood vessels
↓ Po_2 detected by chemoreceptors in carotid and aortic bodies	Vasoconstriction to increase total peripheral resistance (TPR) and arterial pressure
↓ Blood volume (e.g., hemorrhage)	Release of vasopressin (ADH) leads to vasoconstriction, which increases TPR and water reabsorption.
↑ Atrial pressure	Release of atrial natriuretic peptide (ANP) to relax vascular smooth muscle to reduce TPR, and increase natriuresis to reduce blood volume

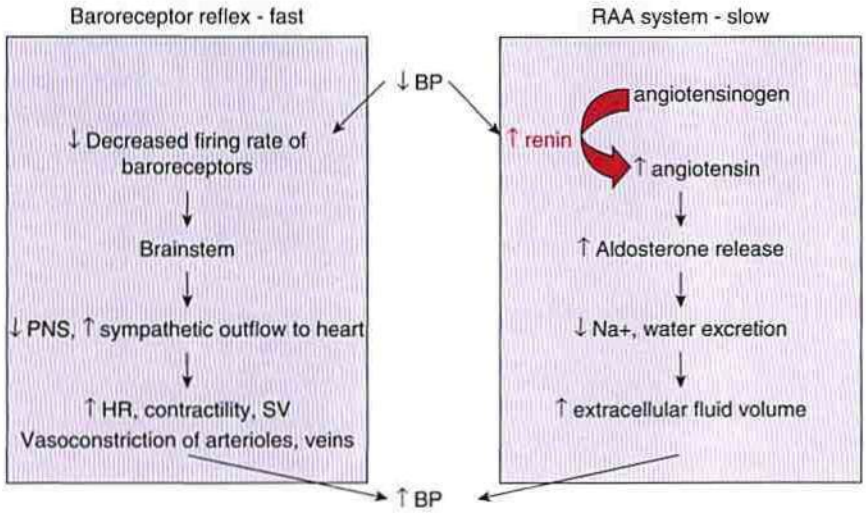


FIGURE 1-28. Effect of decreased BP on baroreceptors and the renin-angiotensin-aldosterone (RAA) system.

Autonomic Nervous System

Sympathetic and PS nervous systems of the ANS affect HR via the SA and AV nodes, conduction velocity, and blood vessel tone through action on β1 and muscarinic acetylcholine receptors (mAChR), respectively (see Table 1-14).

Renin-Angiotensin-Aldosterone System: Long-Term Regulation of Blood Pressure

Decreased BP activates the RAAS. Renin is secreted and increases conversion of angiotensinogen to angiotensin, which causes increased release of aldosterone from the adrenal cortex, decreased Na and water excretion, and resulting increased extracellular fluid volume and BP (see Figure 1-28).

Autoregulation

Each organ has a different mechanism to maintain constant blood flow over a wide range of perfusion pressures (see Table 1-15). Except for the pulmonary vasculature, in which hypoxia induces vasoconstriction, hypoxia causes vasodilation in all other organs, thus increasing delivery of blood and O_2 to starved tissues.

TABLE 1-14. Autonomic effects on the heart and blood vessels.

	Sympathetic	Parasympathetic
Heart Rate Conduction Velocity at AV node Contractility	↑ via β_1 receptor	↓ via mAch receptor (contractility decreased in atria only)
Vascular Smooth Muscle	Constriction via α_1 receptor Relaxation via β_2 receptor	

KEY FACT

Conduction velocity through the AV node is controlled by:

- SNS: Increased conduction of action potentials from atria to ventricles, which may compromise ventricular filling time
- PNS: Decreased conduction → increased PR interval

KEY FACT

Circulation through organs:

Liver: Largest share of systemic cardiac output

Kidney: Highest blood flow per gram of tissue

Heart: Largest arteriovenous O_2 difference; increased O_2 demand met by increasing coronary blood flow.

TABLE 1-15. Autoregulation in Various Organs

Organ	Factors Determining Autoregulation	Portion of the Cardiac Output Received (%)
Heart	Local metabolites: O_2, adenosine, NO; enhanced during mechanical compression in systole	5
Brain	Local metabolites: CO_2 (pH)	15
Kidneys	Myogenic and tubuloglomerular feedback	20
Lungs	Hypoxia-induced vasoconstriction	100
Skeletal muscle	Local metabolites: lactate, adenosine, K^+ (also His, bradykinin)	20
Skin	Sympathetic stimulation	5

HEMODYNAMICS AND PERIPHERAL VASCULAR CIRCULATION

KEY FACT

- Arterioles: Site of highest resistance in the CV system
- Capillaries: Largest total cross-sectional and surface area (remember, this facilitates gas exchange!)
- Veins: Highest proportion of blood in the CV system

Physical factors such as blood flow, velocity, resistance, and capacitance govern blood flow within the circulatory system. The components of blood and the circulatory system (i.e., types of vasculature) are reviewed briefly.

Blood

Normal adult blood composition is illustrated in Figure 1-29. Note that serum = plasma – clotting factors (e.g., fibrinogen).

Components of the Vasculature

The vasculature includes arteries, arterioles, capillaries, venules, and veins, each of which has different composition and function (see Table 1-16).

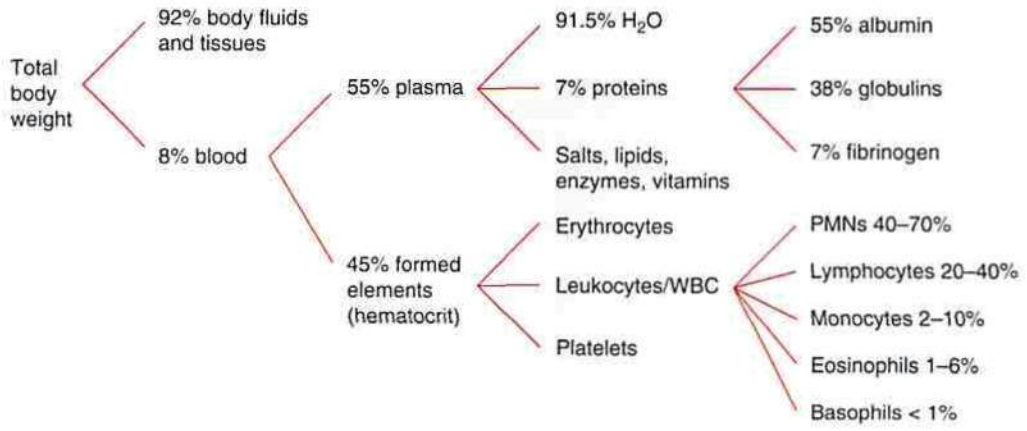


FIGURE 1-29. Normal adult blood composition.

TABLE 1-16. Function and Composition of the Vasculature

	Composition	Pressure	Function
Artery	Thick-walled with elastic tissue, smooth muscle	High	Deliver oxygenated blood to tissues
Arteriole	Smooth muscle with innervation from autonomic nerve fibers	High	Smallest branches of arteries
Capillary	Single layer of endothelial cells, thin-walled	Low	Exchanges nutrients, water, and gases with surrounding tissues
Venule		Low	Formed from merged capillaries
Vein	Thin-walled	Low	The largest vein, the vena cava, returns blood to the heart

Hemodynamic Parameters

Velocity of Blood Flow (v)

$$v = Q/A$$

v = velocity (cm/sec)
Q = blood flow (mL/min)
A = cross-sectional area (cm^2)

Velocity is directly proportional to blood flow (increased blood flow → increased velocity), and inversely proportional to area; i.e., blood flow velocity is higher in the aorta (smaller cross-sectional area) than in the capillaries (larger total cross-sectional area).

Blood Flow (Q)

$$Q = \Delta P/R$$

Relationship is analogous to Ohm's law (I = V/R), where

Q (blood flow or cardiac output, mL/min)	↔	I (current)
ΔP (pressure gradient, mmHg)	↔	V (voltage)
R (resistance, mmHg/mL/min)	↔	R

Blood flow is inversely proportional to blood vessel resistance and can be hormonally controlled. **Histamine** and **bradykinin** mediate arteriolar dilation and venous constriction, promoting blood flow to the site of their secretion, whereas serotonin causes arteriolar constriction. **Prostaglandins** have different effects—prostacyclin is a vasodilator in several vascular beds, but thromboxane A2 acts as a vasoconstrictor.

- **Coronary blood flow:** During systole, coronary arteries are compressed → increased coronary vascular resistance → decreased coronary blood flow. The largest proportion of coronary blood flow occurs during diastole.

Resistance (R)

$$\text{Resistance} = \frac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \frac{8\eta(\text{viscosity}) \times \text{length}}{\pi r^4} \text{ (Poiseuille's Law)}$$

FLASH FORWARD

Viscosity (η) depends on hematocrit, which is increased in:

- Polycythemia
- Hyperproteinemic states (e.g., multiple myeloma)
- Hereditary spherocytosis

Resistance is inversely proportional to the fourth power of the blood vessel radius, so increasing the radius by 2 times decreases the resistance by a factor of $2^4 = 16$! Resistances in parallel or series can be calculated with the following equations:

- In **parallel** (e.g., systemic circulation in which each organ is supplied by an artery that branches off the aorta)

$$1/R_{total} = 1/R_a + 1/R_b + \ldots + 1/R_n$$

- In **series** (e.g., the arrangement of blood vessels in a given organ; the incoming large artery becomes arterioles, capillaries, and veins that are arranged in series)

$$R_{total} = R_{artery} + R_{capillaries} + R_{veins}$$

- The same volume of blood flows through each set of vessels; i.e., blood flow through the largest artery is the same as through all the capillaries.

Arterioles have the largest proportion of resistance, and they are responsible for the largest drop in perfusion pressure.

KEY FACT

Velocity $v = Q/A$

Blood flow $Q = \Delta P/R$

Resistance

$$R = \frac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \frac{8\eta(\text{viscosity}) \times \text{length}}{\pi r^4}$$

Capacitance $C = V/P$

Capacitance (Compliance)

$C = V/P$

C = capacitance (mL/mmHg)
V = volume (mL)
P = pressure (mmHg)

Capacitance describes how distensible a blood vessel is and is inversely related to elastance. Since veins are more compliant than arteries, more blood is stored in veins than in arteries. During aging, vessels stiffen and become less compliant.

Laminar versus Turbulent Flow

Laminar flow is streamlined (i.e., travels in a straight line). Turbulent flow is not and causes audible vibrations (bruits). Turbulence is increased by:

- Decreased blood viscosity (e.g., anemia)
- Increased blood velocity (e.g., narrower vessel, increased cardiac output)

Capillary Fluid Exchange

Fluid movement is determined by osmotic and hydrostatic pressures in the capillary and interstitial space, which are known as Starling forces (see Figure 1-30). These include:

- P_c = Capillary pressure: Tends to move fluid out of the capillary
- P_i = Interstitial fluid pressure: Tends to move fluid into the capillary
- π_c = Plasma colloid osmotic pressure: Tends to move fluid into the capillary
- π_i = Interstitial fluid colloid osmotic pressure: Tends to move fluid out of the capillary

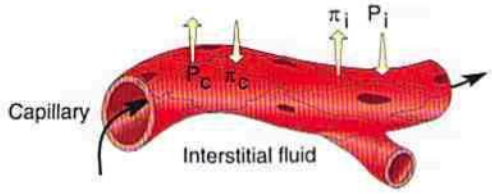


FIGURE 1-30. Capillary fluid exchange.

Net Filtration Pressure (P_{NET})

Sum of the Starling forces (note that the force is negative if entering the capillary and positive if leaving the capillary):

$$P_{net} = [(P_c - P_i) - (\pi_c - \pi_i)]$$

Net Fluid Flow (J_v, mL/min)

Determined by P_{net} and K_f, the filtration constant (capillary permeability). This relationship is known as the **Starling equation**. A positive J_v means net fluid movement out of the capillary (filtration).

$$J_v = K_f * P_{net} = K_f[(P_c - P_i) - (\pi_c - \pi_i)]$$

Lymphatics

Lymph from right side of upper body empties into right lymph duct. All other lymph empties via the **thoracic duct** into the venous system. Lymph has the same composition as the surrounding interstitial fluid.

Edema

Occurs when volume of interstitial fluid > capacity of lymphatics and filtration; caused by increased K_f, increased P_c, and/or decreased π_c (these all increase J_v) (see Table 1-17 and Table 1-18).

TABLE 1-17. Causes and examples of edema.

Cause	Examples
↑ P_c	Increased venous pressure Standing, which causes edema in the dependent limbs
↓ π_c	Decreased plasma protein concentration secondary to: ▪ Decreased synthesis (liver disease) ▪ Decreased intake (protein malnutrition) ▪ Increased excretion (nephrotic syndrome)
↑ K_f	Burn Inflammation

TABLE 1-18. Types of Edema

Types of Edema	Transudate	Exudate
Mechanism	Increased capillary pressure (P_c) or decreased oncotic pressure (π_c) ▪ Fluid from the vessel is either pushed out or leaves based on differences in osmotic pressure.	More permeable vessels (increased K_f) ▪ The vessel becomes leakier; therefore both protein and fluid leave.
Composition of fluid	Protein-poor	Protein-rich

ELECTROCARDIOGRAPHY

ECGs are recordings of electrical impulses flowing through the heart. They provide information about cardiac structure and function. These impulses follow a distinct pathway, known as the cardiac conduction system:

- An electrical impulse begins at the **SA node**.
- The impulse traverses the atria to the **AV node**.
- The AV node conducts the impulse slowly, which allows atrial contraction to be completed before ventricular depolarization and contraction occur.
- Conduction continues through the **bundle of His** and into **right and left bundle branches**.
- Bundle branches divide into **Purkinje fibers**, which stimulate myocardial cell contraction.

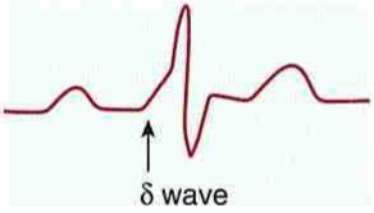


FIGURE 1-31. Characteristic delta wave seen in Wolff-Parkinson-White syndrome.

Wolff-Parkinson-White Syndrome

If an accessory pathway from the atrium to the ventricle is present, electrical impulses bypass the AV node and ventricles partially depolarize earlier. This condition, known as Wolff-Parkinson-White syndrome, has a characteristic delta wave on ECG (see Figure 1-31) and may result in reentry current, leading to supraventricular tachycardia.

Electrocardiogram Lead System

Twelve leads record along set axes—six leads on the **frontal** plane (I, II, III, aVR, aVL, and aVF) and six on the **transverse/horizontal** (V_1–V_6) plane of the body, also known as the chest or precordial leads (see Figure 1-32). ECG is recorded on 1-mm graph paper at a speed of 25 mm of recording paper per second. Each millimeter (small box) corresponds to 0.04 second, and 5-mm grid lines indicate 0.2 second.

KEY FACT

Locations and corresponding leads:
Inferior = II, III, aVF
Anterior = V_1–V_6

Electrocardiographic Intervals

There are three major intervals:

- **PR interval.** Measured from onset of P wave to onset of QRS; depends on both conduction velocity through AV node and HR.
- **QRS interval.** Measured from beginning to end of QRS complex.
- **QT interval.** Measured from beginning of QRS to end of T wave.

KEY FACT

Increased HR → decreased PR interval.

Normal interval lengths are listed in Table 1-19.

TABLE 1-19. Electrocardiographic Intervals

Interval	Normal Range
PR	0.12-0.20 sec (3-5 small boxes)
QRS	≤ 0.10 sec (≤ 2.5 small boxes)
QT	Corrected QT* ≤ 0.44 sec

*Corrected QT = QT/√(R-R), R-R = distance between two QRS complexes

ARRHYTHMIAS

Arrhythmias are abnormalities of electrical rhythm that result from alterations of **impulse conduction, impulse formation**, or both.

Disturbances of Impulse Conduction

Disturbances can be due to a delay or failure of conduction and can occur in any part of the cardiac conduction system, in particular, in the AV node (**AV block**) and bundle branches (**bundle-branch block**).

AV Block

- **First-degree AV block:** Conduction between atria and ventricles is delayed due to an abnormal AV node. Prolonged PR interval (≥ 0.20 sec), with each P wave followed by a QRS complex (see Figure 1-33). Due to a wide variety of causes, including vagal stimulation, β-receptor antagonists, and infiltrative or degenerative conditions (e.g., amyloidosis, sarcoidosis)
- **Second-degree AV block:** Intermittent or cyclical failure of impulse conduction from atria to ventricles. If it occurs in a regular pattern, it is often described as the ratio of the number of P waves (conducted and nonconducted) to the number of QRS complexes per cycle (e.g., 3:2, 4:3, 2:1). The two types—Mobitz type I (aka Wenckebach) and type II—can be differentiated by PR intervals (see Table 1-20 and Figure 1-34).
- **Third-degree (complete) AV block:** Failure of any impulses to be conducted from atria to ventricles. Atria and ventricles beat independently of

KEY FACT

In Mobitz type I second-degree AV block, PR intervals progressively lengthen before the dropped beat. In Mobitz type II, PR intervals are constant.

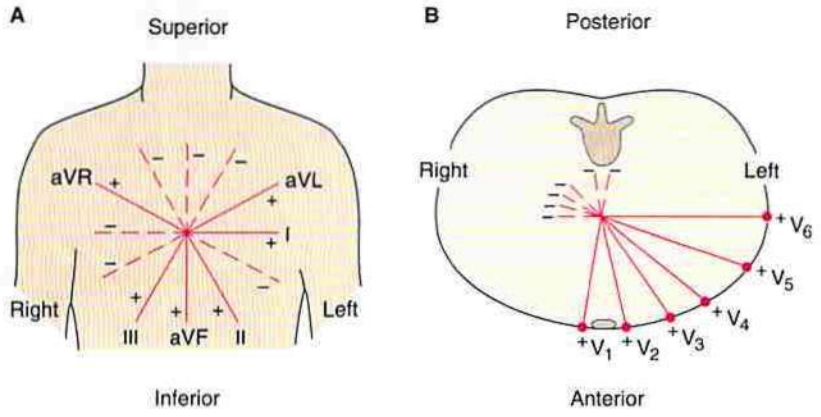


FIGURE 1-32. (A) Frontal and (B) precordial leads. (Modified, with permission, from Kasper DL, Braunwald E, Fauci AS, et al, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 1312.)

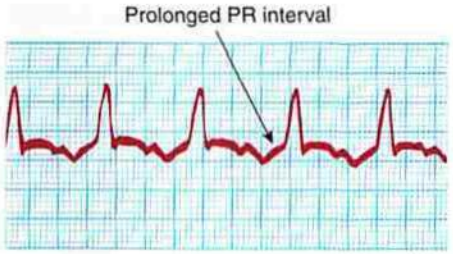


FIGURE 1-33. First-degree AV block.

each other (**AV dissociation**), in which ventricles are depolarized by AV nodal or ventricular escape rhythm. As a result, both P waves and QRS complexes are present, but there is **no relationship** between P waves and QRS complex (see Figure 1-35). Atrial rate is faster than ventricular rate. Usually treated with a pacemaker.

Bundle-Branch Block

Failure of impulse conduction through one of the bundle branches. Affected ventricle depolarizes much more slowly. For example, in left bundle-branch block (LBBB), the RV depolarizes before the LV.

Disturbances of Impulse Formation

Disturbances of impulse formation are due to an ectopic impulse originating from outside the SA node, which depolarizes the heart and causes an ectopic beat. These may originate from latent pacemaker cells (in the AV nodal area or His-Purkinje system) outside the SA node (**escape beats**), from the atria (**supraventricular arrhythmia**), or from the ventricles (**ventricular arrhythmia**).

Escape Beats and Rhythms

Normally, pacemaker cells outside of the SA node (i.e., AV node and His-Purkinje system) remain latent since their rate of depolarization is slower than

TABLE 1-20. Comparison of Mobitz Type I and II Second-Degree AV Block

	Mobitz Type I (Wenckebach)	Mobitz Type II
Description	Intermittent failure of AV conduction	Sudden, unpredictable loss of AV conduction
ECG finding	Progressive lengthening of the PR interval until a beat is "dropped" (P wave not followed by QRS complex)	Constant PR intervals before dropped beats
Anatomic site of block	AV node	Almost always below the AV node; frequently associated with bundle-branch block
Complications	Usually asymptomatic; very rarely progresses to third-degree (complete) AV block	Often progresses to third-degree AV block; may require prophylactic pacing

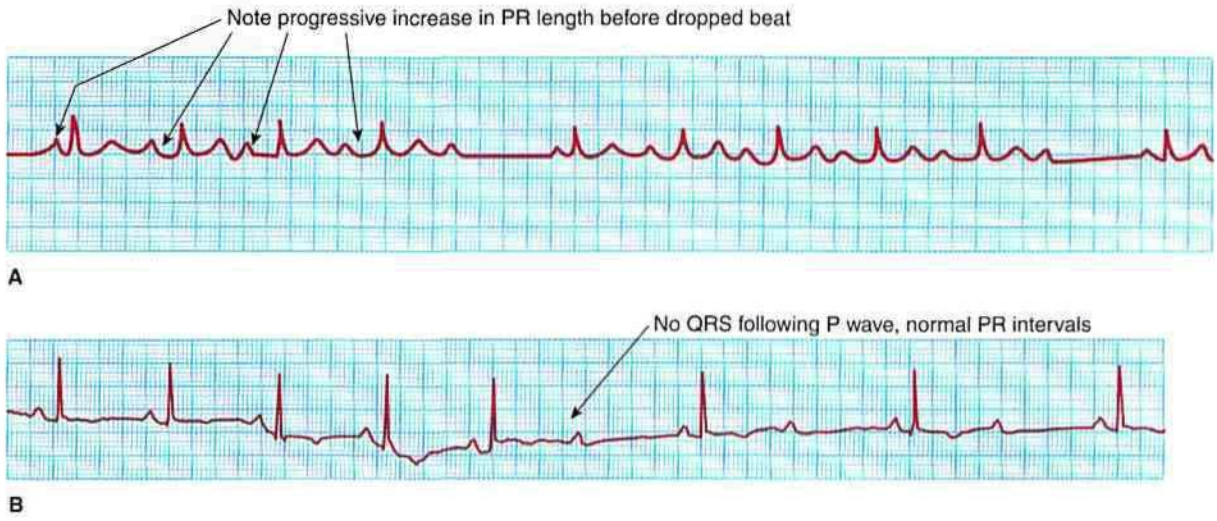


FIGURE 1-34. ECG tracings of second-degree AV block. (A) Mobitz type I, and (B) Mobitz type II.

that of the SA node; they are depolarized by the SA nodal impulse before they reach threshold and depolarize spontaneously.

However, if the SA nodal impulse fails to depolarize these pacemaker cells, they may reach threshold and produce an escape beat. Two types—junctional and ventricular escape beats—may occur, depending from where they originate.

- **Nodal or junctional escape beats.** Originate from the AV nodal area and are conducted through the His-Purkinje system to the ventricles, producing a normal QRS complex. Junctional escape rhythms can be seen in third-degree (complete) AV block. Typical rate: 45–60/min.
- **Ventricular escape beats.** Originate from an ectopic ventricular focus (often Purkinje fibers). Abnormal QRS complex. Ventricular escape rhythm can be seen in third-degree (complete) AV block. Typical rate: 35–40/min.

Supraventricular Arrhythmias

These originate above the ventricles and usually have normal QRS complexes.

- **Paroxysmal supraventricular tachycardia (PSVT).** Regular, rapid (150–250/min) arrhythmia that originates in atria or AV node. Often due to reentrant pathway in the AV node.

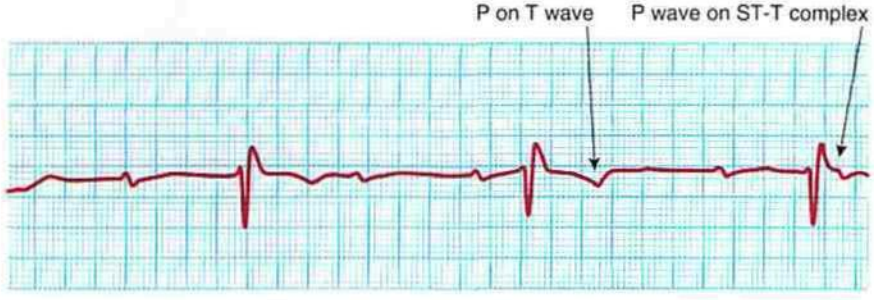


FIGURE 1-35. ECG tracing of third-degree (complete) AV block.



FIGURE 1-36. ECG tracing of atrial flutter.

- **Atrial flutter.** Regular, rapid (250–350/min) arrhythmia originating from the atria. ECG shows a rapid succession of identical, back-to-back atrial depolarization waves, giving a "sawtooth" appearance (see Figure 1-36). Caused by re-entry over a large anatomically fixed circuit. Not all atrial impulses are transmitted to ventricles because the AV node is in refractory period (physiologic AV block)—2:1 or 4:1 conduction.
- **Atrial fibrillation.** Irregularly irregular, rapid (350–600/min) impulses from multiple atrial foci depolarize the atria. Chaotic and erratic baseline with no discrete P waves and irregularly spaced QRS complexes (see Figure 1-37). Associated with right or left atria enlargement. Atrial contraction ineffective, causing decreased cardiac output.

KEY FACT

A mural thrombus adheres to a wall of the heart or major artery. MS is a risk factor for LA mural thrombus.

VENTRICULAR ARRHYTHMIAS

KEY FACT

Impulses that travel through the His-Purkinje system are associated with normal QRS complexes. Impulses that originate in the ventricles are conducted slowly through ventricular myocardium and produce an abnormal QRS complex.

Arrhythmias that originate in ventricles and therefore have abnormal QRS complexes.

- **Premature ventricular contraction (PVC).** Ectopic ventricular pacemaker produces an ectopic beat before the next sinus beat occurs.
- **Ventricular tachycardia (VT).** Ectopic impulses originate in ventricles at a regular, rapid rate (100–250/min). Most frequently caused by re-entry mechanism. Can deteriorate into ventricular fibrillation. **Torsades de pointes** is a form of VT in which QRS amplitude and axis change cyclically. Occurs most often in patients with prolonged QT interval.
- **Ventricular fibrillation.** Rapid, irregular ventricular depolarization due to impulses that originate from multiple ectopic ventricular foci. Completely erratic rhythm with no identifiable waves (see Figure 1-38). Fatal arrhythmia without immediate defibrillation.

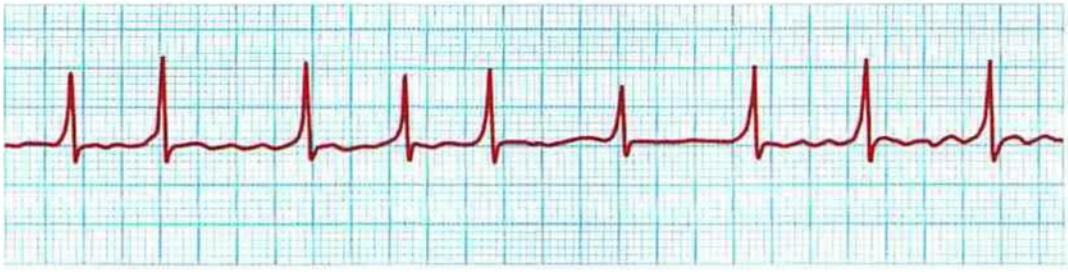


FIGURE 1-37. ECG tracing of atrial fibrillation.

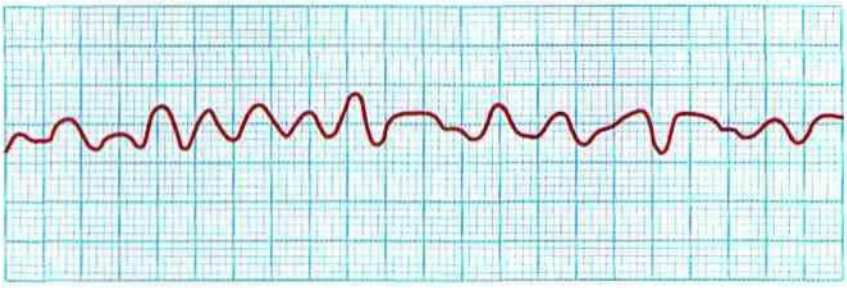


FIGURE 1-38. ECG tracing of ventricular fibrillation.

Pathology

HYPERTENSION

Hypertension affects more than 20% of the population and is a major risk factor for many CV diseases. It is defined as a sustained systolic pressure > 140 mmHg and/or a diastolic pressure > 90 mmHg. Risk factors include **African American** race, obesity, **diabetes**, advanced age, **oral contraceptives**, family history, excessive alcohol consumption, and **cigarette** smoking (see Table 1-21).

KEY FACT

The most common cause of atrial fibrillation in the United States is hypertension.

Primary (Essential) Hypertension

Primary hypertension is the most **common** type (95% of cases) of hypertension. Although there is no identifiable cause, genetics, excessive salt intake, and increased **adrenergic tone** have all been implicated in primary hypertension. Risk factors include increasing age, obesity, diabetes, smoking, genetics, and race (African American > Caucasian > Asian) because of reduced sodium excretion.

CLINICAL CORRELATION

For each 10-mmHg systolic or 5-mmHg diastolic pressure increase above 115/75 mmHg, the CV disease risk doubles.

Complications include atherosclerosis, **stroke**, **chronic kidney disease**, LV hypertrophy (see Figure 1-39), **heart failure**, retinopathy, aortic dissection, and ischemic heart disease (IHD).

DIAGNOSIS

BP of > 140/90 mmHg, confirmed on **three** separate occasions, or a single reading of > 170/110 mmHg. Since it is a diagnosis of exclusion, rule out secondary hypertension.

TABLE 1-21. Stages of Hypertension

	SYSTOLIC (mmHg)	DIASTOLIC (mmHg)
Normal	< 120	< 80
Prehypertension	120–139	80–89
Stage 1	140–159	90–99
Stage 2	≥ 160	≥ 100

KEY FACT

Thiazide diuretics are the initial drug of choice for treatment of primary hypertension.

CLINICAL CORRELATION

ACE inhibitors have been proven to lower mortality and morbidity in diabetic hypertensives. They decrease renal hypertension by lessening efferent arteriolar vasoconstriction and therefore intraglomerular pressure, preventing eventual proteinuria.

FLASH FORWARD

Decreased vascular tone → increased renin production → angiotensin I → angiotensin II → vasoconstriction → hypertension and increased aldosterone secretion. Aldosterone → sodium and water retention → hypertension.

KEY FACT

Pheochromocytoma presents with the triad of hypertension, diaphoresis, and tachycardia.

FLASH BACK

Coarctation of the aorta is a constriction of the aortic segment usually distal to the left subclavian artery that leads to high BP in the upper extremities, low BP in the lower extremities, and differential cyanosis.

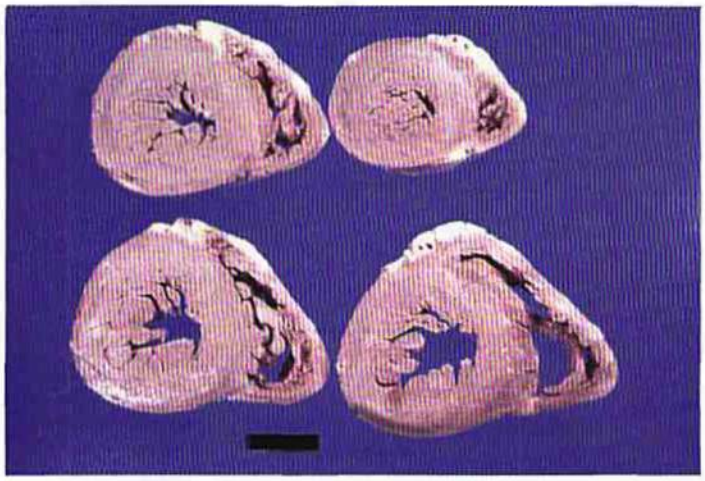


FIGURE 1-39. LV hypertrophy. Horizontal sections of the LV in the above picture show concentric hypertrophy often seen in hypertension. (Image courtesy of PEIR Digital Library [http://peir.net].)

Treatment

Initial treatment includes weight loss, decreased alcohol intake, increased exercise, reduced Na intake, and smoking cessation. All of the above are otherwise known as therapeutic lifestyle modifications.

Medical therapy involves the use of diuretics, β-adrenergic antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, or α-adrenergic antagonists.

Secondary Hypertension

Secondary hypertension is increased systemic arterial pressure as a result of other identifiable conditions. Features of secondary hypertension include onset of hypertension at **ages** < 20 or > 50 years old, BP > 180/110 mmHg, abdominal bruits, and a **family history** of renal disease or **uncontrolled hypertension** despite maximal doses of three antihypertensive agents. Etiologies include:

- **Renal artery stenosis:** Etiologies include atherosclerosis (older patients, usually bilateral) and **fibrous dysplasia**, a "beaded appearance" on arteriogram (young women).
- **Renal parenchymal disease:** Treat with ACE inhibitors, which slow progression.
- Oral contraceptive pill use, glucocorticoids, phenylephrine, and NSAIDs (preferentially constrict the afferent arteriole).
- Pheochromocytoma: Adrenal tumor secreting catecholamines.
- Primary aldosteronism (Conn's syndrome): Aldosterone-producing tumor causes **triad** of hypertension, hypokalemia, and metabolic acidosis (increased aldosterone, decreased renin).
- Hyperthyroidism.
- Cushing's syndrome.
- Coarctation of the aorta.

Presentation

Patients are usually asymptomatic but can present with symptoms of end-organ damage such as chest pain, peripheral edema, vision changes, and claudication. On physical exam, check for signs of end-organ damage.

- **Cardiac:** An S4 heart sound due to increased resistance to ventricular filling and peripheral edema.
- **Renal:** Microalbuminuria, proteinuria.
- **Vascular:** Carotid bruits, hyaline arteriosclerosis, abdominal bruits.
- **Ophthalmologic:** Loss of venous pulsations, arteriovenous nicking, hemorrhages, and papilledema.

Diagnosis

A good history and physical exam are necessary in hypertension. Clinical features of secondary causes of hypertension, if they can be elicited, are extremely helpful. These can include sweating and palpitations for pheochromocytoma, an abdominal bruit for renal artery stenosis, temperature intolerance, lack of energy and bradycardia/tachycardia for thyroid disorders, or absent femoral pulse for coarctation of the aorta. Lab studies include TSH, plasma renin activity, urinalysis, and serum creatinine. Diagnostic tests are those for each individual disease.

Treatment

Includes treating the underlying etiologic cause Nonpharmacologic treatment includes weight loss, sodium restriction, smoking cessation, exercise, and reduction in alcohol intake. Antihypertensive medications include ACE inhibitors, ARBs, diuretics, vasodilators, calcium channel blockers, and α- and β-blockers.

Malignant Hypertension

Malignant hypertension is a severe, **rapid increase** in BP, usually > 240/120 mmHg, associated with **organ damage** ("flea-bitten kidneys"). It is most often seen in young African American males. Clinically it is characterized by LV hypertrophy, increased diastolic pressure, papilledema, and retinal hemorrhages, as well as chest pain, dyspnea, angina, or headache. End-organ damage results in CV damage, pulmonary edema, azotemia, fundal hemorrhages, encephalopathy, seizures, and coma.

ARTERIOSCLEROSIS

Arteriosclerosis comprises a group of diseases that involve arterial wall thickening and loss of elasticity. They are divided into three categories.

Mönckeberg's Arteriosclerosis

A benign **medial** calcification of medium-sized (muscular) arteries that usually affects radial, ulnar, tibial, uterine, or femoral arteries in the elderly. It is normally asymptomatic and **benign** (unless associated with atherosclerosis).

Arteriolosclerosis

Affects the **intima** of small arterioles and arteries and is most often seen in the elderly and in those with diabetes, metabolic syndrome, or hypertension.

Microscopically there are two types of arteriolosclerosis:

- **Hyaline** arteriolosclerosis: **Protein** deposits seen in **essential hypertension** are visualized as pink arterial wall thickening with luminal narrowing in diabetics. It is due to advanced glycosylation end products being deposited in the vessel's basement membrane. In hypertensives, it results from an increased pressure in the arteries that forces proteins into the wall causing increased muscle and elastic tissue (see Figure 1-40).

CLINICAL CORRELATION

Hypertensive urgency = BP > 180/120 mmHg with no end-organ damage
Hypertensive emergency = BP > 180/120 mmHg with end-organ damage

KEY FACT

Mönckeberg's does not obstruct arterial flow since the intima is not involved.

MNEMONIC

Mönckeberg is **M**edial calcification of the **M**edium-sized arteries.

FLASH BACK

Metabolic syndrome is a group of risk factors in a single individual that increases risk for CV disease. These include insulin resistance, hypertension, abdominal obesity, dyslipidemia, and prothrombotic states.

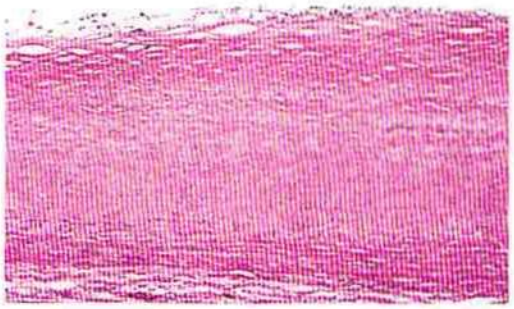


FIGURE 1-40. Hyaline arteriosclerosis. There is vast fibrotic intimal thickening and subendothelial foam cells. (Image courtesy of PEIR Digital Library [http://peir.net].)

FLASH FORWARD

In the kidney, **hyaline arteriosclerosis** is termed **benign nephrosclerosis,** and **hyperplastic arteriosclerosis** is termed **malignant nephrosclerosis.**

- **Hyperplastic** arteriolosclerosis: Seen in **malignant hypertension**, is visualized as an increase in smooth muscle proliferation and basement membrane duplication leading to "**onion skinning**" (concentric wall thickening). Effects are especially prevalent in the renal arterioles (see Figure 1-41).

Atherosclerosis

Usually affects **medium** and **large** arteries such as the aorta, coronary arteries, carotid arteries, cerebral arteries, and popliteal arteries. Lipid deposition, fatty streaks, and fibrous plaques form in the **intima** of medium to large arteries. Risk factors are divided into major and minor categories.

- **Major:** Hyperlipidemia, hypertension, smoking, diabetes, and obesity.
- **Minor:** Male gender, oral contraceptives/decreased estrogen, increased age, sedentary lifestyle, stress, elevated homocysteine level, family history, and infections (***Chlamydia pneumoniae***).

KEY FACT

Hyperlipidemia is defined as an excess of fat in the blood. These lipids can be triglycerides, cholesterol, cholesterol esters (compounds), or phospholipids.

Pathogenesis

Endothelial cell injury → macrophages/platelets adhere to damaged endothelium and release cytokines → smooth muscle hyperplasia/migration of cells to the tunica intima → macrophages form **foam cells** plus smooth muscle → fibrous cap develops → fibrous cap (plaque) calcifies dystrophically and ulcerates → platelets adhere to the ulcer, causing vessel thrombosis (see Figure 1-42)

KEY FACT

C-reactive protein (CRP) is a marker of inflammation, as seen in unstable plaques.

KEY FACT

Oxidized LDL is more atherogenic.



FIGURE 1-41. Hyperplastic arteriosclerosis. Notice how the basement membrane duplication and smooth muscle proliferation resemble the layers of an onion. (Image courtesy of PEIR Digital Library [http://peir.net].)

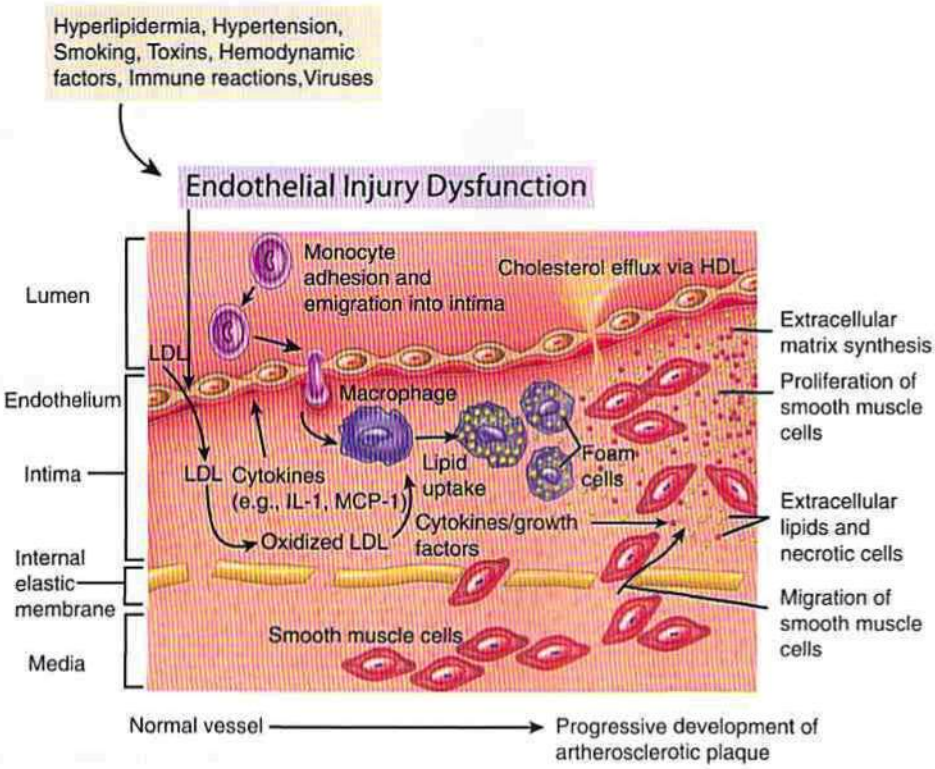


FIGURE 1-42. Pathogenesis of atherosclerosis.

Gross/Microbiology

- Fatty streaks are flat and yellow and on microscopy contain **foam cells** (lipid-laden macrophages).
- Fibrous plaques are elevated white plaques that contain a necrotic core of cholesterol, lipids, foam cells, and debris surrounded by a fibrous cap of collagen, smooth muscle, and lymphocytes (see Figure 1-43).

KEY FACT

Aneurysm formation is often found below the level of the renal arteries since there are fewer vasa vasorum in the media of these vessels, leading to increased impact of ischemia.

Complications

Plaque rupture, unstable angina, **MI**, death, **stroke**, aneurysm formation due to artery wall degeneration, transient ischemic attacks, renal artery ischemia,

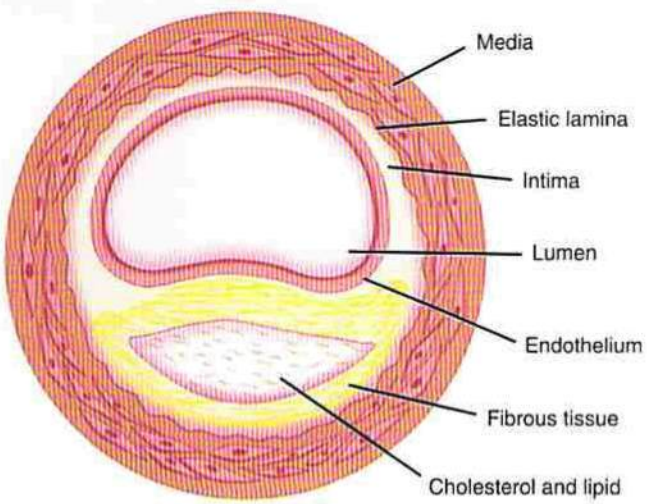


FIGURE 1-43. Fibrous plaque.

peripheral vascular occlusive disease, impotence, **claudication**, proximal renal thrombosis → RAAS activation and hypertension

MYOCARDITIS

KEY FACT

The most common etiology of myocarditis is viral.

Myocarditis is inflammation of the heart muscle secondary to multiple possible etiologies. Infection is common and can be **viral** or bacterial. Viral, including coxsackie B, rubella, and cytomegalovirus, is the most common. The condition can often be diagnosed by endocardial biopsy showing lymphocytic infiltrates.

KEY FACT

Bacterial myocarditis is rare in patients without immunodeficiency.

Bacteria such as ***Staphylococcus aureus***, ***Corynebacterium diphtheriae***, and ***Haemophilus influenzae*** can cause myocarditis.

Myocarditis in those with HIV can be caused by toxoplasmosis or Kaposi's sarcoma metastasis. Chagas' disease (caused by ***Trypanosoma cruzi***), Lyme disease, acute renal failure, rheumatic fever, lupus, and drugs such as doxorubicin may also cause myocarditis.

PRESENTATION

Patients may present with any of the following: Chest pain, edema, and breathlessness from congestive heart failure (CHF); palpitations from arrhythmias, fever, diarrhea, and fatigue due to viral illness; a muffled S1, an S3, and MR murmur.

DIAGNOSIS

FLASH BACK

Virulence factors of ***S. aureus*** include **protein A** to inhibit phagocytic engulfment and **catalase** to enhance survival in phagocytes.

ECG shows diffuse T-wave inversions and ST-segment elevations, which can mimic an MI or pericarditis. Biopsy is the gold standard, demonstrating edematous myocardial interstitium with lymphocytic infiltrate. CK-MB and troponin may also be elevated.

TREATMENT

Supportive therapy for acute heart failure using diuretics, ACE inhibitors, or nitrates is often beneficial. Viral myocarditis requires symptomatic treatment such as NSAIDs for inflammation and diuretics for ventricular failure. Bacterial myocarditis requires antibiotics.

ENDOCARDITIS

Endocarditis is an inflammation of the lining of the heart and heart valves.

Infective Endocarditis

KEY FACT

Right-sided endocarditis should suggest IV drug abuse. Since drugs are injected into the veins, the bacteria go to the right heart first.

The heart valves are avascular; therefore, if bacteria adhere, WBCs cannot be recruited to the area. Endocarditis can be acute or subacute.

FLASH FORWARD

Septic emboli can cause ring-enhancing brain lesions, as can tumors, pyogenic abscesses, toxoplasmosis, and tuberculosis.

Acute infective endocarditis usually affects **normal heart valves** and is most often caused by **S. *aureus*** or IV drug abuse because of the ability of **S. *aureus*** to colonize normal valves.

Subacute infective endocarditis usually colonizes a **previously damaged valve** (after oral surgery or poor dentition). It is most often caused by ***Streptococcus viridans*** (see Table 1-22).

TABLE 1-22. Bacterial Causes of Endocarditis

Risk Factor/Presenting Factor	Bacteria to Consider
Prosthetic device	*Staphylococcus epidermidis*
Colon cancer	*Streptococcus bovis*
Dental procedure	*Streptococcus viridans*
GI surgery	*Enterococcus*
Total parenteral nutrition	Fungal
Alcoholics or the homeless	*Bartonella henselae*
Fastidious and culture negative	HACEK organisms

HACEK = *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella.*

Presentation

Fever, chills, weight loss, systemic emboli, petechiae, **Janeway's lesions** (painless peripheral hemorrhages on the palms and soles), **Osler's nodes** (small, painful subcutaneous nodules on the fingers and toes), **splinter hemorrhages** (linear streaks under the fingernails and toenails), **Roth's spots** (retinal seeding), and **valvular involvement** (mitral > aortic > tricuspid).

Diagnosis

Duke criteria include positive serial blood cultures, prior endocardial involvement, IV drug use, fever, vascular or immune phenomena, and valvular lesions on echocardiography.

Treatment

IV antibiotics targeted to the specific organism. For acute endocarditis, start antibiotics empirically—nafcillin and gentamicin provide good coverage. For subacute endocarditis, obtain blood cultures before starting antibiotics. Choices include ampicillin + gentamicin for native valves, and vancomycin, gentamicin, and rifampin for prosthetic valves.

Marantic Endocarditis

Nonbacterial endocarditis (nonbacterial thrombotic endocarditis; NBTE) occurs when small, sterile fibrin vegetations deposit on the heart valves of people with debilitating disease. This is a paraneoplastic syndrome whereby mucin-secreting tumors (usually of the colon or pancreas) cause disease in which mucin seeds the heart valves, yielding a platelet-sticky nidus of infection. A major complication is **sterile** peripheral **emboli**, which can lead to cerebral infarct. Marantic endocarditis has a poor prognosis.

Libman-Sacks Endocarditis (LSE)

Libman-Sacks endocarditis is autoantibody damage to the heart valves from systemic lupus erythematosus. Sterile vegetations form on **both sides of the heart valves**. Often the patient is asymptomatic, but the condition can be picked up by the presence of a heart murmur.

KEY FACT

Staphylococcus epidermidis mostly affects prosthetic valves within the first 6 months. After that, ***S. aureus*** and ***S. viridans*** are the most likely culprits.

MNEMONIC

Roth's **R**etina, **O**sler's "**O**uch" (signifying tender finger pads), **Jane**way's hands and **Splinter** in your finger

FLASH FORWARD

SLE can lead to antiphospholipid syndrome, which causes a hypercoagulable state. Suspect if a patient's history is significant for multiple spontaneous abortions.

MNEMONIC

LSE is caused by SLE.

Carcinoid Syndrome

Carcinoid tumors release an increased amount of serotonin, which leads to thickening, contraction, and decreased mobility of the **right-sided valves**, as well as blood vessel dilation. The left side of the heart is protected by serotonin inactivation in the lungs. The difference between **carcinoid syndrome** and **carcinoid tumors** is as follows:

- **Carcinoid syndrome** is a group of symptoms associated with carcinoid tumor. Its origin is most commonly in the terminal ileum and the tumor is large enough to cause systemic effects such as abdominal pain, flushing, diarrhea, and wheezing.
- **Carcinoid tumor** is most commonly found in the appendix, but in general the tumor is too small to be symptomatic.

FLASH BACK

Vitamin $\mathbf{B_1}$ also leads to beri-beri (see as **B**er**1**-**B**er**1**).

Diagnosis

Serotonin metabolite, 5-hydroxindoleacetic acid (5-HIAA) levels in the urine are elevated. CT, MRI, and indium-111 pentetreotide scan (OctreoScan) are all also used in diagnosis.

Treatment

Surgery to remove the tumor is often first-line treatment. Octreotide (Sandostatin) injections can be used in those patients in whom surgery is not an option.

FLASH BACK

Chagas' disease is caused by ***T. cruzi***, which is transmitted by the reduviid bug.

CARDIOMYOPATHIES

See Table 1-23.

Dilated/Congestive

The dilated variant represents approximately 90% of nonischemic cardiomyopathies. Echocardiography often reveals four-chamber enlargement.

CLINICAL CORRELATION

Complications of dilated cardiomyopathy include cardiac arrhythmias, mural thrombi, CHF, bundle-branch blocks, and death.

Etiologies include: idiopathic (most common), alcohol, thiamine deficiency, coxsackievirus B, Chagas' disease, HIV, cocaine, doxorubicin, Lyme disease, sarcoidosis, hypothyroidism, Wegener's granulomatosis, acromegaly, and peripartum cardiomyopathy.

TABLE 1-23. Cardiomyopathies

	Dilated	Hypertrophic	Restrictive
Etiology	Idiopathic, ethanol, coxsackievirus B, cocaine, Chagas' disease, peripartum	Autosomal dominant	Senile/primary amyloidosis, sarcoidosis, Loeffler's endomyocarditis
Clinical presentation	↓ EF and JVP, fatigue, cardiomegaly, dyspnea	Dyspnea, angina, S4, syncope	Peripheral edema, dyspnea, ascites, JVD
Special notes	Most common form on chest x-ray: balloon heart	Young athletes' chest x-ray: banana-shaped LV	

Presentation

Can present as right or left heart failure. Decreased EF, jugular venous distension, edema, orthopnea, hepatomegaly, or cardiomegaly

Diagnosis

X-ray shows an enlarged cardiac silhouette with pulmonary congestion. **Echocardiography** is the key diagnostic study and shows a dilated LV and decreased EF.

Treatment

Similar to treatment of CHF: Digitalis, β-blockers, ACE inhibitors, ARBs, diuretics, vasodilators, or heart transplantation. Anticoagulation is used to prevent emboli.

Hypertrophic Cardiomyopathy (HCM)

It is usually an autosomal-dominant disorder in which asymmetric septal hypertrophy causes a decrease in LV compliance and diastolic dysfunction. Blood flows at an increased velocity over the hypertrophied septum, creating negative pressure which draws the anterior mitral leaflet into the outflow tract causing subaortic obstruction to outflow via the Venturi effect. HCM can lead to sudden cardiac death seen in some **young athletes**.

KEY FACT

Hypertrophic cardiomyopathy is the most common cause of sudden unexplained death in young athletes.

Presentation

Syncope, dyspnea, S4 cardiac gallop due to an atrial kick into the noncompliant ventricle, cardiomegaly secondary to aberrant fibers in the myocardium, systolic murmur of MV regurgitation, and pain relieved by squatting and exacerbated by strenuous exercise.

KEY FACT

Any maneuver that decreases end-diastolic volume will increase the murmur heard in hypertrophic cardiomyopathy because the decreased volume leads to a decreased chamber size and increased obstruction. Examples include the Valsalva maneuver, exercise, and amyl nitrate. MVP has the same characteristics.

Diagnosis

The x-ray shows a dilated LA. Echocardiography is normally used for diagnosis and shows asymmetric hypertrophy, mitral valve regurgitation, and diastolic dysfunction.

Treatment

The goal is to maintain ventricular filling in order to prevent obstruction. β-Blockers and calcium channel blockers are often used to slow the HR and increase diastolic filling time, as well as decrease myocardial O_2 consumption. Implantable cardioverter defibrillators (ICDs) are often implanted in high-risk patients to prevent sudden cardiac death.

Restrictive Cardiomyopathy

The least common type of cardiomyopathy. It is caused by diseases that infiltrate the myocardium to impede diastolic filling of the heart. Common causes include **sarcoidosis, amyloidosis**, hemochromatosis, Loeffler's endomyocarditis (most common worldwide), endocardial fibroelastosis (children), postradiation fibrosis, glycogen storage diseases (Pompe's disease), inborn errors of metabolism (Fabry's disease, Gaucher's disease), and scleroderma.

KEY FACT

Primary amyloidosis is a disorder in which amyloid light chain protein fibers are deposited in tissues and organs, impeding their function.

Presentation

Dyspnea, weakness, exercise intolerance, peripheral edema, ascites, JVD, S4 gallop, pulsus paradoxus, CHF, and arrhythmias from conduction defects.

KEY FACT

Loeffler's endocarditis is usually seen in young male immigrants from the rain forests of Africa, Asia, and South America. Treatment is symptomatic.

Diagnosis

X-ray shows mild cardiomegaly. Echocardiography shows **thickening** of cardiac structures.

Treatment

There is no effective therapy except to treat the underlying disease. Heart transplantation is an option.

CONGESTIVE HEART FAILURE

CHF is defined as the inability of the heart to generate a sufficient cardiac output to meet the metabolic demands of the body. It is a syndrome or diagnosis, not a specific disease. Heart failure can be the final manifestation of most cardiac disease, from hypertension to cardiomyopathy. There is an increasing incidence in the United States due to the growing aging population and prolonged survival after cardiac insults. CHF is usually attributed to left heart failure; however, left and right heart failure often occurs concurrently.

KEY FACT

An S3 heart sound is caused by vibration and turbulence as blood fills a ventricle that already has excess fluid due to systolic dysfunction.

Left-Sided Heart Failure

There are two major causes of left-sided heart failure: Systolic dysfunction due to impaired contractility and/or increased afterload, or diastolic dysfunction due to impaired ventricular filling, relaxation, or compliance (see Table 1-24).

Presentation

Patients typically present with dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema, reduced renal perfusion, and an S3 heart sound. Most of these are due to failure of LV output and increased pulmonary venous pressure.

KEY FACT

Cor pulmonale is an alteration of the structure and function of the right side of the heart secondary to chronic lung disorders, resulting in pulmonary arterial hypertension.

Microscopically, intra-alveolar hemosiderin-laden macrophages (heart failure cells), alveolar edema, and cardiac monocyte hypertrophy are seen. Complications include pulmonary congestion, cardiogenic shock, and hyperaldosteronism secondary to RAAS activation.

TABLE 1-24. Etiology of Left-Sided Heart Failure

	Systolic Dysfunction		Diastolic Dysfunction	
	Impaired Contractility	Increased Afterload	Ventricular Relaxation	Impaired Ventricular Filling
Etiologies	Myocardial infarction	Hypertension	Ventricular hypertrophy	Mitral stenosis
	Myocardial disease	Aortic stenosis	Cardiomyopathy	Tamponade
	Myocardial ischemia Volume overload, mitral or aortic regurgitation	Hypertrophic cardiomyopathy	Myocardial ischemia	Pericardial constriction
Signs and symptoms	Dyspnea, orthopnea, fatigue, palpitations, ascites, S3 gallop		Filling defect with increased or normal ejection fraction; S4 gallop, edema, hepatomegaly	



FIGURE 1-44. Nutmeg liver. The congested centrilobular veins which are surrounded by a paler region seen in the liver on the left look similar to the inside of a nutmeg, seen on the right, hence the name nutmeg liver. (Image courtesy of PEIR Digital Library [http://peir.net].)

Treatment

Acute treatment involves relieving dyspnea and congestion with O_2, diuretics, nitrates, and morphine. Long-term management includes counteracting rise in hormone levels with β-blockers, ACE inhibitors, and ARBs.

Right-Sided Heart Failure

The most common cause of right-sided heart failure is left-sided heart failure. Other causes include cor pulmonale and pulmonary or tricuspid valve disease.

Presentation

Patients usually present with splenomegaly, hepatomegaly/ascites ("nutmeg" liver), edema, and jugular venous distention. Renal hypoxia as well as right-sided pump failure leads to fluid retention clinically seen as pitting edema (first in the ankles), pleural effusions, and ascites (see Figures 1-44 and 1-45).

Complications include cardiac cirrhosis due to long-standing congestion.

Treatment

Involves ACE inhibitors, which decrease afterload and prevent aldosterone-mediated salt and water retention. ACE inhibitors have been shown to **decrease mortality** in CHF patients. Diuretics are also a mainstay in CHF treatment by preventing volume overloading. Digoxin is not used, as the EF in diastolic dysfunction is normal.

ANEURYSMS

Aneurysms are congenital or acquired **abnormal dilatations** of either an artery or vein due to weakness of the vessel wall. There are many types of aneurysms (discussed below). Complications of aneurysms include thrombus formation, erosion into nearby structures, and rupture leading to hypotension, shock, or death.

KEY FACT

"Nutmeg" liver refers to congestion of the centrilobular veins surrounded by a paler region.

KEY FACT

Angiotensin receptor blockers are similar to ACE inhibitors in their effects; however, they do not increase bradykinin levels as do ACE inhibitors and thus do not have the side effect of dry cough.

MNEMONIC

To remember the treatments of acute decompensated CHF think:

L: Lasix (furosemide)
M: Morphine
N: Nitrates
O: O_2
P: Position (better to sit up)

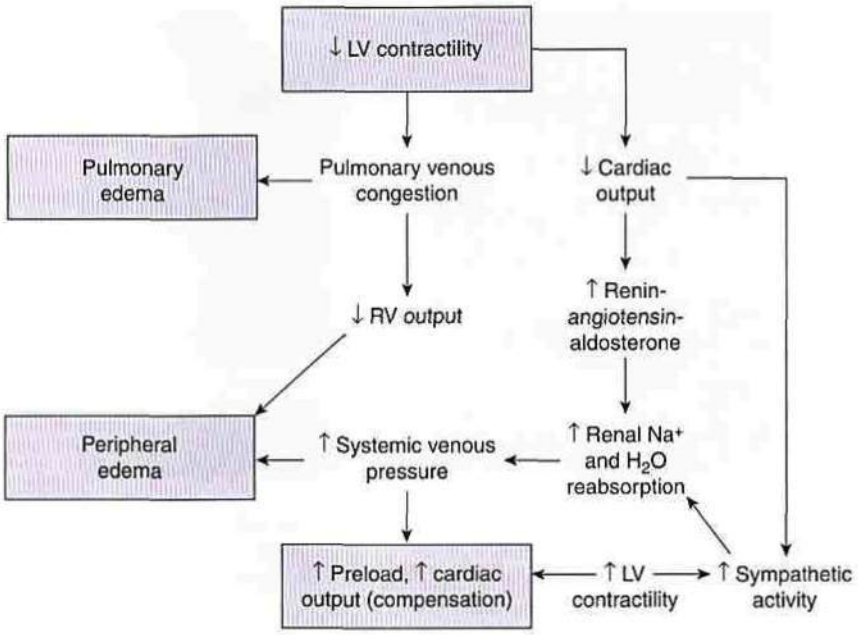


FIGURE 1-45. Pathophysiology of CHF.

FLASH BACK

Primary syphilis presents with a painless, hard chancre. Secondary syphilis presents with condylomata lata, low-grade fever, and lymphadenopathy. Tertiary syphilis presents with aortic insufficiency and Argyll Robertson pupils (pupils accommodate but do not react).

Atherosclerotic Aneurysms

Pathogenically caused by atheroma formation leading to weakening of the media. Usually due to atherosclerotic disease or coronary artery disease (CAD) and associated with **hypertension**. The most common location for these aneurysms is the **abdominal aorta** between the renal arteries and iliac bifurcation (infrarenal = comparatively fewer vasa vasorum).

Syphilitic Aneurysms

Syphilis is a STD that has primary, secondary, and tertiary stages. Seen in the tertiary stage, **syphilitic aortitis** is characterized by medial necrosis and **obliterative endarteritis** of the vasa vasorum, creating a functional deficit similar to atherosclerotic aneurysm. Usually involves the **ascending aorta** and aortic root. Involvement of the AoV can lead to aortic insufficiency.



FIGURE 1-46. Circle of Willis. Note the two aneurysms demarcated white. (Image courtesy of PEIR Digital Library [http://peir.net].)

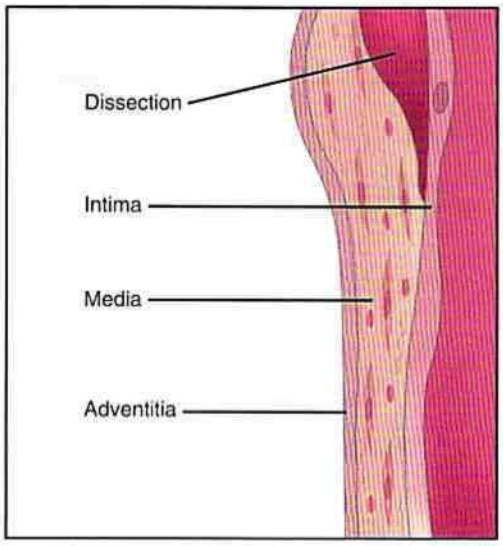


FIGURE 1-47. Dissection. A dissection occurs between the intima and media of a vessel.

Berry Aneurysms

These are small, congenital, saccular lesions seen most often in the **circle of Willis**. Although not present at birth, these lesions develop at congenital sites of medial weakness at the **bifurcations of cerebral arteries.** They are associated with polycystic kidney disease and rupture can lead to subarachnoid hemorrhage (see Figure 1-46).

KEY FACT

A patient with a subarachnoid hemorrhage presents with "the worst headache of my life."

Dissecting Aneurysms

Luminal blood dissects the medial layers through a longitudinal intimal tear usually found in the ascending aorta. Often this is due to **cystic medial necrosis**, in which there is degeneration of elastic tissue and muscle in the tunica media. Predisposing factors include hypertension or **Marfan's syndrome**. Patients present with a severe tearing pain (dissection), which can result in proximal aortic rupture leading to cardiac tamponade (see Figure 1-47).

Mycotic Aneurysms

Usually due to bacterial infection (most often *Salmonella*) involving the abdominal aorta.

Microaneurysms

These are small aneurysms usually seen in diabetes and hypertension.

KEY FACT

Erythema marginatum is seen as nonpruritic, serpiginous, erythematous rings on the patient's trunk and extremity, usually sparing the face.

Arteriovenous Fistula

This is an abnormal communication between an artery and a vein, usually secondary to trauma. The diversion of blood can result in **ischemic changes**, increased venous pressure leads to **aneurysm** formation, and hypervolemia leading to **high-output cardiac failure**.

RHEUMATIC FEVER

Rheumatic fever is a multisystem inflammatory disease that may occur following pharyngeal infection with **group A β-hemolytic streptococci**. It usually affects children aged 5–10 years. It has been postulated that the streptococcal antigens elicit antibody production that cross-reacts with cardiac antigens.

KEY FACT

Sydenham's chorea is an involuntary, purposeless contraction of the trunk muscles and extremities.

MNEMONIC

Group A **STREP** also causes rheumatic fever:
Sydenham's chorea
Transient migratory arthritis
Rheumatic subcutaneous nodules
Erythema marginatum
Pancarditis

MNEMONIC

JONES PEACE.

Major criteria:
Joints: migratory arthritis
Carditis: new-**O**nset murmur
Nodules, subcutaneous: extensor surfaces
Erythema marginatum
Sydenham's chorea
Minor criteria:
PR interval, prolonged
ESR elevated
Arthralgias
CRP elevated
Elevated temperature (fever)

TABLE 1-25. Jones Criteria

Major Criteria	Minor Criteria
Migratory polyarthritis	Arthralgia (most common)
Carditis	Fever
Subcutaneous nodules	High ESR/CRP
Erythema marginatum	Long PR interval
Syndenham's chorea	ASO titer
	High WBC count
	Anemia

Two major criteria or one major and two minor criteria are needed for diagnosis.

PRESENTATION

Classically, patients complain of a pharyngeal infection 1–4 weeks prior, and present with symptoms from the Jones criteria (see Table 1-25 and Figure 1-48).

Acute Rheumatic Heart Disease

The most serious complication of rheumatic fever. It can be divided into:

- Fibrinous pericarditis.
- Myocarditis (**Aschoff's bodies**) focal interstitial myocardial inflammation in which collagen and fibrinoid material are surrounded by macrophages (**Anitschkow's cells**), lymphocytes, plasma cells, and multinucleated giant cells (**Aschoff's cells**) (see Figure 1-49).



FIGURE 1-48. Rheumatic subcutaneous nodules often seen on the extensor surface. (Reproduced, with permission, from South-Paul JE, Matheny SC, Lewis EL, *Current Diagnosis & Treatment in Family Medicine*, New York: McGraw-Hill, 2004: 280.)



FIGURE 1-49. Acute rheumatic heart disease. Note the typical multinucleated Aschoff cells, which are modified histiocytes. An Aschoff body is an area of fibrinoid necrosis surrounded by lymphocytes and macrophages. (Courtesy of O. Rambo as printed in McPhee SJ, Papadakis MA, Tierney Jr, LM, *Current Medical Diagnosis & Treatment* 2008, 47th ed, New York: McGraw-Hill, 2008.)

- Endocarditis: The valve leaflets become red and swollen and small verrucae (rubbery fibrin vegetations) form along the lines of closure. Eventually the valves become fibrotic, thickened, and calcified. Valvular disease can lead to either insufficiency or stenosis. Most often affected are the mitral and AoVs since they see the greatest pressure gradient.

KEY FACT

Aschoff's bodies contain both Aschoff's cells and Anitschkow's cells.

Chronic Rheumatic Heart Disease

Mitral and aortic valvular fibrosis causes valve thickening and calcifications, fusion of commissures, and short, thick chordae tendineae. The chronic form can lead to mitral stenosis (MS), MR, aortic regurgitation, and CHF. It can also predispose to infectious endocarditis.

KEY FACT

Myocarditis leading to cardiac failure is a cause of death in acute rheumatic fever.

Diagnosis

Usually made though clinical suspicion and fulfilling the Jones criteria. A positive streptococcal antibody test can verify prior infection and echocardiography can help in diagnosing CV problems.

Treatment

Symptomatic and involves:

- Treatment of group A streptococci with penicillin
- Use of steroids or salicylates for pain and inflammation
- Digitalis for heart failure
- Haloperidol for Sydenham's chorea

CLINICAL CORRELATION

The murmur of mitral valve prolapse (MVP), often seen in patients with Marfan's and young women, is exaggerated by the Valsalva maneuver. Endocarditis prophylaxis is used prior to dental procedures in these patients.

CLINICAL CORRELATION

An S3 occurs in early diastole and implies volume overload in older adults. It can be normal in children and young adults.

KEY FACT

An S3 occurs in early diastole and implies volume overload in older adults. It can be normal in children and young adults.

CLINICAL CORRELATION

Tricuspid regurgitation is a blowing holosystolic murmur heard at the left lower sternal border that increases with inspiration due to the increase in venous return to the right side of the heart.

HEART MURMURS

Murmurs are normally generated by turbulent blood flow. If there are hemodynamic or structural changes in the heart, laminar flow may become turbulent, thus creating a heart sound. The most common hemodynamic or structural changes that occur to the heart are increased flow, decreased valvular area, regurgitation, dilated chambers, and shunting. Heart sounds are auscultated in four places on the anterior chest wall (see Figure 1-50).

Murmurs can be divided into three groups (see Table 1-26): Systolic (between S1 and S2), diastolic (between S2 and S1), and continuous (throughout the cycle or between S1 and the next S1).

Mitral Regurgitation (MR)

Insufficiency of the mitral valve allows for backflow of blood from the LV into the LA. Acute causes of MR include papillary muscle rupture, endocarditis, or ruptured chordae tendineae. Chronic causes include **rheumatic heart disease**, ischemic cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, MVP, endocardial fibroelastosis, or endocarditis.

Presentation

Clinically patients can present with LV failure (dyspnea, orthopnea) and dilated LA due to increased volume. Chronic disease can lead to right-sided failure (edema or ascites).

On physical examination, an **S3** and a **holosystolic**, high pitched, blowing murmur are heard best at the apex, radiating toward the left axilla. The murmur is holosystolic since LV pressure is always greater than LA pressure in systole. The increased flow in the LA can lead to increased LA pressure and **pulmonary edema** (see Figure 1-51).

Diagnosis

ECG changes include LV hypertrophy and LA enlargement. Echocardiography shows LA and LV enlargement.

Treatment

The goal is to increase forward flow and decrease pulmonary venous hypertension. Medications include diuretics, ACE inhibitors, and digitalis. MV repair or replacement is usually required for symptomatic severe MR.

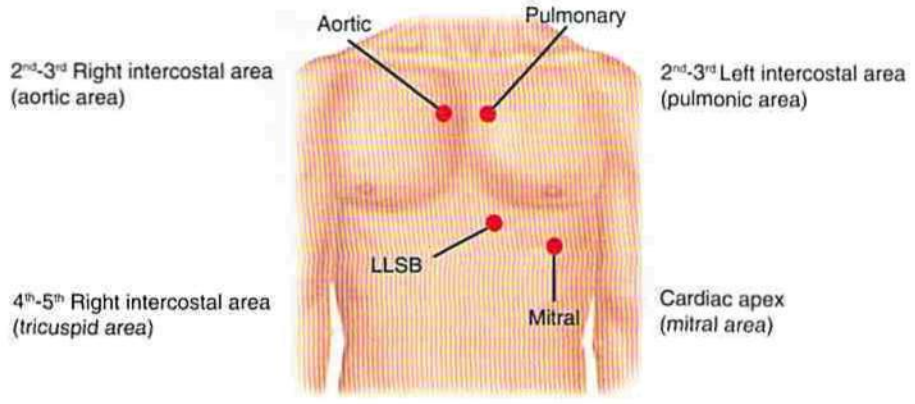


FIGURE 1-50. Cardiac physical examination areas.

TABLE 1-26. Classification of Murmurs

Systolic			Diastolic		Continuous
Ejection	Holosystolic	Late Systolic	Early	Late	
Aortic stenosis	MR	MVP	Aortic regurgitation	Mitral stenosis	PDA
Pulmonic stenosis	Tricuspid regurgitation VSD	HCM	Pulmonic regurgitation	Tricuspid stenosis	

Aortic Stenosis (AS)

Usually due to thickening and calcification of the valves with age, rheumatic heart disease, or it can be due to congenital bicuspid valves.

Presentation

- Patients can have angina, syncope, or dyspnea from CHF.
- Crescendo-decrescendo systolic ejection murmur that begins shortly after the S1 heart sound. The small gap between the end of S1 and the beginning of the murmur corresponds to the isovolumic contraction phase of the LV in which both the mitral and AoV are closed. Once the AoV opens, the murmur intensifies as the LV pressure increases (crescendo) and then subsides as the LV relaxes (decrescendo). The high-frequency murmur is best heard in the aortic area and usually radiates to the carotids (in the direction of turbulent blood flow) (see Figures 1-52 and 1-53).
- Weak and delayed pulse at the jugular vein due to stenosis (pulsus parvus et tardus).

MNEMONIC

Aortic **S**tenosis **C**omplications:

Angina
Syncope
CHF

Diagnosis

Echocardiography shows thickened AoV with decreased systolic opening and LV hypertrophy.

CLINICAL CORRELATION

Pulmonic stenosis is also a systolic ejection murmur that can radiate to the neck or shoulder and is loudest in the second and third right intercostal space.

Treatment

Surgical correction or balloon valvuloplasty. Endocarditis prophylaxis is necessary.

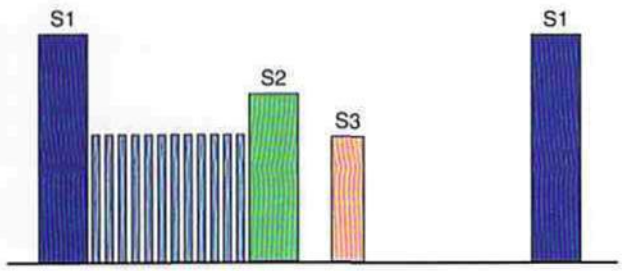


FIGURE 1-51. Mitral regurgitation. Note the holosystolic murmur followed by an S3 heart sound.

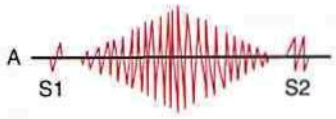


FIGURE 1-52. Aortic stenosis. Notice the crescendo-decrescendo pattern that is due to blood being forced through the narrowed AoV.

FLASH BACK

A single ventricular chamber is divided into two chambers between the fourth and eighth weeks of gestation as muscle tissue forms from the apex to the cushion.

Ventricular Septal Defect (VSD)

A developmental defect in the interventricular septum that allows the two ventricles to communicate. VSDs most often occur in the membranous intraventricular septum.

Presentation

A defect in this septum leads to left-to-right shunting of blood, which can lead to increased pulmonary blood flow and pulmonary artery pressure. As a congenital defect, it is most often found in infants who present with a harsh systolic murmur, fatigue with feeding, poor growth, and respiratory infections.

KEY FACT

Left-to-right shunting can lead to increased pulmonary and right atrial pressure, which can cause a right-to-left shunt. This is called Eisenmenger's syndrome.

Diagnosis

The VSD murmur is a harsh, nonradiating holosystolic murmur best heard at the fourth and fifth intercostal area. The smaller the VSD, the more turbulent the flow through it, resulting in a louder murmur over the entire precordium. Extremely large VSDs may be entirely silent (see Figure 1-54).

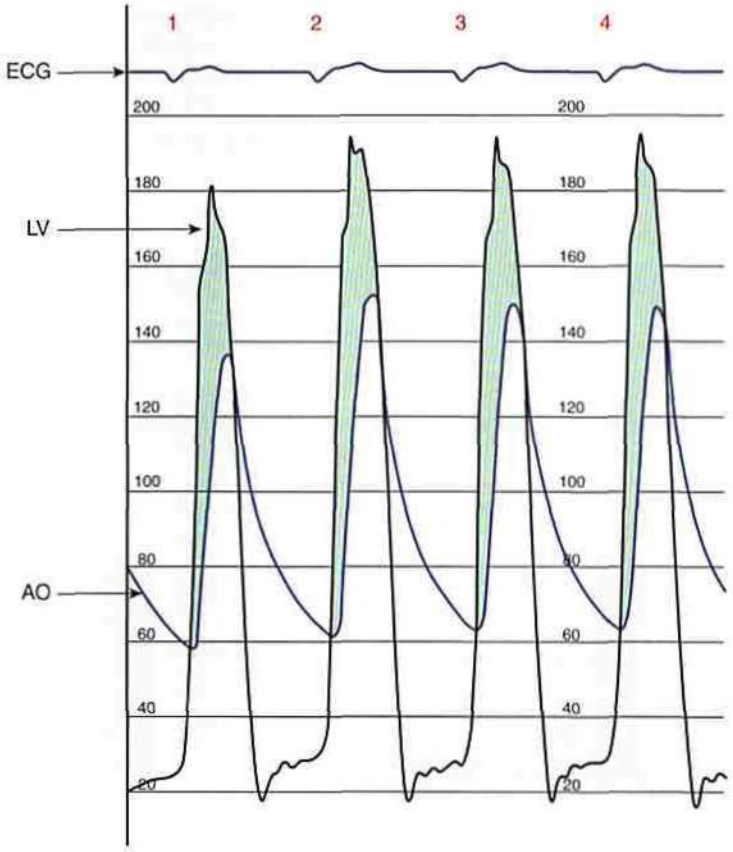


FIGURE 1-53. Aortic stenosis pressure tracing. Here it can be seen that left ventricular pressure is greater than aortic pressure throughout the systolic cycle. This increase in pressure is due to aortic stenosis. The shaded area is the pressure gradient between the LV and the aorta.

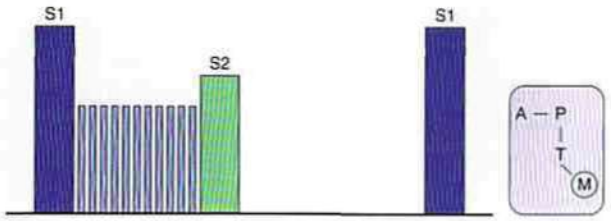


FIGURE 1-54. VSD.

TREATMENT

Surgical correction of the defect

Mitral Valve Prolapse (MVP)

A common syndrome that affects up to 7% of women aged 14–30 years. Often called floppy valve disease, it occurs when the MV leaflets do not close properly and billow into the LA during ventricular systole. It can be an autosomal-dominant disorder or acquired as part of a connective tissue disorder. The normal collagen and elastin are replaced by myxomatous connective tissue.

KEY FACT

Connective tissue disorders such as Marfan's syndrome, SLE, the mucopolysaccharidoses, hypothyroidism, and Ehlers-Danlos syndrome can present with MVP.

PRESENTATION

- Usually asymptomatic; however, it can cause chest pain, palpitations, labored breathing, or fatigue. The murmur heard in MVP is a late systolic murmur preceded by a midsystolic click that corresponds to the tensing of the mitral leaflet/chordae tendineae as they are forced into the LA. The murmur corresponds to the regurgitation of blood from the LV into the LA (see Figure 1-55).

The Valsalva maneuver decreases preload, while squatting increases preload.

Any maneuver that decreases the volume of the LV, such as Valsalva or standing, will allow the prolapse to occur sooner, causing an increase in the intensity of the murmur. Squatting, which will increase venous return, will increase ventricular volume, helping to maintain tension on the chordea tendineae and allow the valve to stay shut longer, thus causing a decrease in the intensity of the murmur.

CLINICAL CORRELATION

MVP and hypertrophic cardiomyopathy are the only two murmurs with this paradoxic relationship. All other murmurs increase in intensity with increased preload (squatting) and decrease in intensity with decreased preload (Valsalva).

DIAGNOSIS

Doppler echocardiography can show systolic displacement of the mitral leaflets.

TREATMENT

Endocarditis prophylaxis and β-blockers for chest pain or arrhythmias. Surgical treatment is rare.

CLINICAL CORRELATION

Often patients with MVP require antibiotic prophylaxis prior to surgical or dental procedures to prevent endocarditis.

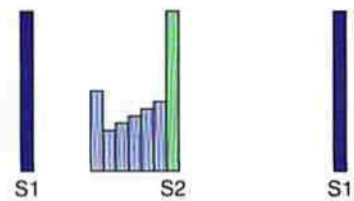


FIGURE 1-55. MVP. Notice the mid-systolic click that precedes the systolic murmur.

Aortic Valve Regurgitation (AR)

Allows backflow of blood from the aorta into the LV during diastole. It can be due to rheumatic heart disease, infectious endocarditis, bicuspid valves, aortic dissection, hypertension, syphilis, or Marfan's syndrome. Regurgitation occurs during diastole, increasing the amount of blood the LV pumps out in the next cycle.

Presentation

Patients typically present with:

- Dyspnea on exertion
- Angina due to shorter diastole and decreased coronary artery filling
- Fatigue
- Wide pulse pressures
- S3 and an early diastolic decrescendo murmur heard best at the second left intercostal space (see Figure 1-56)
- Austin Flint murmur, a mid-diastolic, low-pitched rumbling that occurs when the regurgitated blood hits the MV leaflet in diastole, preventing an opening snap (differentiating AR from MS)

AR → increased LV volume → increased LV diastolic pressure → increased LA and pulmonary pressure → pulmonary edema.

Chronic AR leads to LV dilatation. This dilatation allows the LV to accommodate more aortic regurgitation without further increases in diastolic pressure. The increase in LV systolic pressure without a concomitant increase in aortic diastolic pressure leads to a **widened pulse pressure**.

CLINICAL CORRELATION

AR patients can have a Corrigan's pulse, i.e., a water-hammer pulse over the carotid with marked distention and collapse.

Diagnosis

Echocardiography showing a dilated LV and aorta and aortic regurgitant flow. Regurgitation can cause a "pseudovalve" or "bird's-nest deformity" on the ventricular septum on pathologic examination.

KEY FACT

Pulmonic regurgitation is usually due to pulmonary artery hypertension. It is also a decrescendo murmur and is heard best in the pulmonic area of the heart.

Treatment

The goal is afterload reduction with ACE inhibitors and vasodilators. Diuretics and digitalis are also used. Valve replacement can help if EF decreases or symptoms develop.

Mitral Stenosis

Almost always due to rheumatic heart disease causing commissural fusion. Other causes, such as endocarditis with large vegetations and calcifications in the elderly, have also been noted as etiologies.

Presentation

The stenotic obstruction in MS impedes LA emptying and leads to a pressure gradient between the LA and LV during diastole. Clinically, patients present with dyspnea, fatigue, and orthopnea. The characteristic murmur of MS is

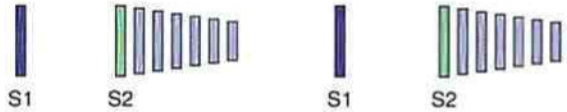


FIGURE 1-56. Aortic regurgitation. The murmur has a decrescendo shape because there is a rapid diastolic relaxation of the LV and therefore a rapid pressure gradient is generated between the high-pressure aorta and the low-pressure ventricle.

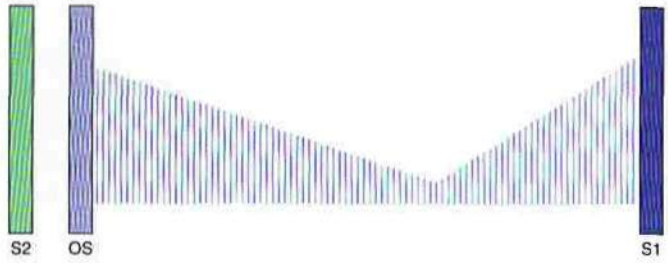


FIGURE 1-57. MS. The opening snap is due to the sudden tensing of the stenotic valve and chordae tendineae upon opening. The decrescendo murmur is caused by turbulent flow across the stenotic valve. The late diastolic intensification of the murmur is attributed to LA contraction at the end of diastole, which increases the pressure gradient between the LA and LV.

a high-pitched opening snap after S2 followed by a decrescendo murmur or rumble that intensifies at the end of diastole and is best heard at the apex (see Figures 1-57 and 1-58).

CLINICAL CORRELATION

Tricuspid stenosis is better heard at the lower sternum and increases with inspiration.

Diagnosis

Echocardiography shows thick MV leaflets and LA enlargement. ECG shows P mitrale (an M-shaped P wave) due to an enlarged atrium (see Figure 1-59).

Treatment

Usually involves diuretics and a salt restricted diet. MV balloon commissurotomy or valve replacement can also be performed if needed. Never use inotropes because MS is **not** equivalent to ventricular failure. Treatment also includes warfarin, β-blockers, and surgery/balloon valvotomy.

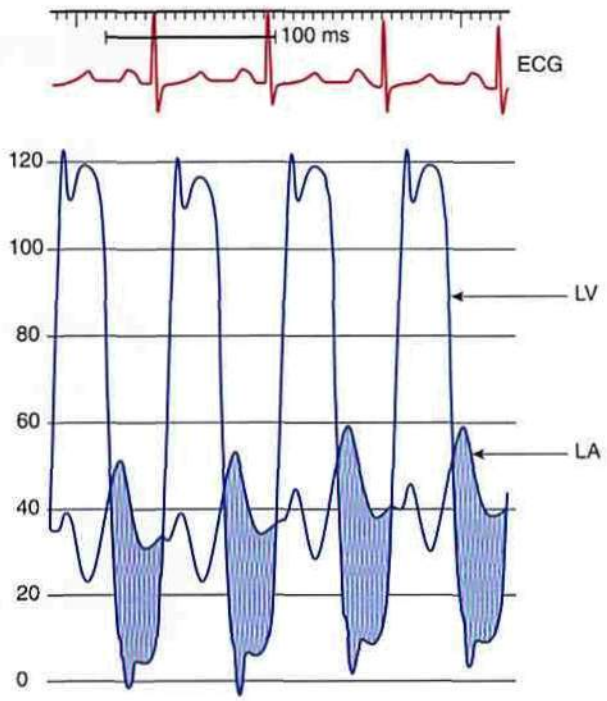


FIGURE 1-58. MS pressure tracing. This figure illustrates the difference in pressure between the LA and LV. Also evident is the increase in pressure at the end of diastole, due to LA contraction. This is why there is a decrescendo-crescendo murmur associated with MS.

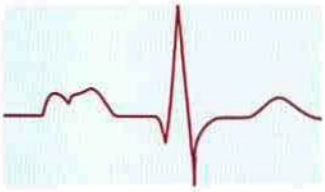


FIGURE 1-59. P mitrale. Note the M-shaped P wave due to an enlarged atrium that is often seen in mitral stenosis.

Patent Ductus Arteriosus (PDA)

CLINICAL CORRELATION

In patients with a PDA, think about congenital rubella and prematurity. A common complication is endarteritis.

A persistent communication between the aorta and the pulmonary artery after birth.

Presentation

CHF and late cyanosis are often seen. Because the aortic pressure is always greater than pulmonary artery pressure in both diastole and systole, the machinery-like murmur is heard throughout the cardiac cycle (see Figure 1-60).

MNEMONIC

Keep open with PG**E**, PG**F** closes.
E for the "**E**mpty" hand when open and F for the "**F**ist" that's closed.

Diagnosis

Doppler echocardiography. Clinically, the well-known machinery-like murmur heard throughout systole and diastole hints at the diagnosis.

Treatment

Indomethacin is often used to close the PDA.

See Table 1-27 for a summary of valvular murmurs.

CARDIAC TUMORS

Primary cardiac tumors are very rare (more rare than secondary tumors) and include myxomas and rhabdomyomas. Most cardiac tumors are metastatic from bronchogenic carcinoma, malignant melanoma, malignant lymphoma, and carcinoma of the pancreas and esophagus.

Cardiac Myxoma

The most common primary tumor in the **adult**. They are benign and found near the fossa ovalis in the **LA** in 90% of adults. They arise from endocardial mesenchymal cells which proliferate and protrude into cardiac chambers. On microscopy, myxoma cells, endothelial cells, and smooth muscle cells are

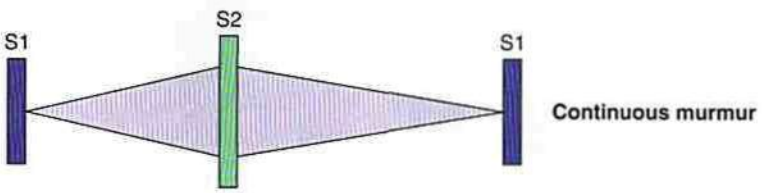


FIGURE 1-60. PDA murmur. Notice how the murmur spans both diastole and systole.

TABLE 1-27. Valvular Heart Disease

Valvular Disease	Etiology	Murmur
MR	**Rheumatic heart disease**, infective endocarditis, myxomatous degeneration, papillary muscle dysfunction, mitral valve prolapse, hypertrophic cardiomyopathy	Holosystolic blowing murmur radiating toward the apex
Mitral stenosis	**Rheumatic heart disease**, calcification, endocarditis	Late diastolic decrescendo rumble preceded by an **opening snap**
MVP	**Connective tissue disorder**, autosomal dominant	Late systolic murmur preceded by a **midsystolic click**
Aortic regurgitation	**Rheumatic heart disease, syphilis, Marfan's syndrome**, aortic aneurysm, bicuspid valve, endocarditis	Early blowing decrescendo diastolic murmur
Aortic stenosis	**Senile** (thickening and calcification), bicuspid AoV	Crescendo-decrescendo systolic ejection murmur

found in a multipolysaccharide background. They may cause tumor emboli or **ball-valve** obstruction and syncopal episodes as they act on the MVs (see Figure 1-61).

Cardiac Rhabdomyoma

The most common primary cardiac tumor in **children**. They usually arise within the myocardium and are associated with **tuberous sclerosis**.

FLASH BACK

Tuberous sclerosis in an autosomal-dominant disorder diagnosed in children that presents with cortical tubers, hamartomas, hypopigmented "ash-leaf" skin lesions, renal angiomyolipomas, and cardiac rhabdomyomas.

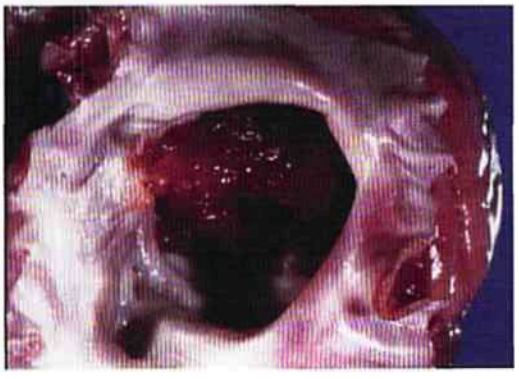


FIGURE 1-61. Cardiac myxoma. This image shows a cardiac myxoma attached by a small pedicle to the left atrial septum. They are normally single, pedunculated, and polypoid. (Image courtesy of PEIR Digital Library [http://peir.net].)

VENOUS DISEASE

Varicose Veins

Varicose veins are tortuous, dilated, superficial vessels that normally involve the lower extremities. More common in women, they are thought to result from increased intraluminal pressure, intrinsic weakness of the vessel wall, and/or congenital defects of the valves that impair forward flow to the heart.

PRESENTATION

Patients have a history of pregnancy, prolonged standing, or obesity. Many people seek treatment for cosmetic reasons; however, symptoms include a dull aching pressure with long periods of standing, swelling and skin ulceration from valvular dysfunction, and thrombosis and hematoma from stasis of blood.

TREATMENT

Treatment includes elevation of the legs, compression stockings to offset the increased venous hydrostatic pressure, and IV sclerosing agents. Surgical vein ligation and therapy is rare and only used in patients with symptomatic recurrent thrombosis or ulcers.

Deep Venous Thrombosis (DVT)

KEY FACT

The most common place for a DVT to develop is in the calves; however, it may also form in the deep veins of the thigh.

Blood clots most often occur in the calf veins, although they can also affect the popliteal, femoral, or iliac veins. Risk factors are summarized in Virchow's triad: Stasis of blood flow, vascular damage, and hypercoagulability (see Table 1-28).

PRESENTATION

Patients can be asymptomatic or present with calf or thigh discomfort, unilateral leg swelling, edema, erythema, and warmth or tenderness on palpation over the vein. Homans' sign or dorsiflexion of the foot producing calf pain is often tested but unreliable.

TABLE 1-28. Virchow's Triad

SIGN OR SYMPTOM	EXAMPLES	PATHOGENESIS
Stasis/turbulence of blood flow	Immobilization (cast applied for bone fracture may cover damaged vessels as well); inactivity (postsurgery, long plane or car rides); hyperviscosity (polycythemia vera); turbulence (aneurysms) particularly common at the carotid bifurcation; deep sea diving (compression of legs and stasis)	Disruption of laminar flow increasing platelet-endothelium contact; there is a build-up of coagulation factors
Vascular damage	Trauma, IV catheters, atherosclerosis	Exposes collagen to increase von Willebrand factor binding and initiate the clotting cascade; endothelial damage also prevents anti-thrombotic secretions
Hypercoagulable state	Clotting disorders (anti-thrombin III deficiency, antiphospholipid antibodies) high-estrogen states (pregnancy, oral contraceptives), smoking, neoplastic disease	Malignancy involves necrotic tumor cells which secrete thrombogenic factors

Diagnosis

Usually made through clinical judgment and laboratory testing. An increased **D-dimer** (fibrin degradation product) is sensitive but not specific. **Venous duplex ultrasonography** uses ultrasound and Doppler to assess blood flow within the vein. This test is both sensitive and specific. The gold standard is angiography.

Treatment

The main objective is to prevent complications such as pulmonary embolism (PE) and post-thrombotic syndrome. Elevation of the extremity helps reduce edema and anticoagulation with heparin is started to prevent thrombus enlargement. For patients who cannot comply with anticoagulation or have medical conditions preventing anticoagulation, an intravascular filter is placed in the IVC to prevent emboli from traveling from the extremity to the lungs.

KEY FACT

Post-thrombotic syndrome results from vascular occlusion and results in persistent edema, skin pigmentation, pruritus, cellulitis, and purpura.

EMBOLI

An embolus is a mass composed of tumor, air, clot, or vegetation, which travels in the bloodstream and is eventually trapped within the vasculature. Thromboembolism refers to fragmented thrombi that are trapped in various parts of human vasculature. These are the most common types of emboli; however, there are other forms such as fat emboli and gas emboli.

Pulmonary Emboli

Pulmonary emboli usually stem from a prior DVT that has fragmented, with small portions traveling through the IVC and into branches of the pulmonary artery.

FLASH BACK

DVT risk factors are stated in Virchow's triad: Stasis of blood, hypercoagulability, and vascular damage.

Presentation

Often clinically silent, this diagnosis is frequently missed in the hospital setting. Patients can present with tachycardia, tachypnea, dyspnea, hemoptysis, cough, and/or chest pain.

Diagnosis

Once clinically suspected, diagnostic tests include a V/Q scan in which there will be a ventilation-perfusion mismatch, spiral CT, pulmonary angiogram, or Doppler ultrasound.

Treatment

Options include anticoagulation therapy with heparin and warfarin or IVC filter placement to prevent future emboli. Thrombolytic therapy is also an option with substances such as tissue plasminogen activator or streptokinase; however, there is an increased risk of bleeding and stroke with thrombolytics.

KEY FACT

Red or hemorrhagic infarcts occur in tissues where there is collateral circulation such as lung, intestine, or post-reperfusion. Pale infarcts occur in solid tissue with a single blood supply, like the brain, kidney, or spleen.

Prognosis

The majority of patients, if correctly diagnosed, have no sequelae. Obstruction of the pulmonary artery can lead to a hemorrhagic pulmonary infarction in which the patient presents with shortness of breath, hemoptysis, and pleuritic chest pain. Sudden death occurs in cases of a saddle embolus and a minority of patients with multiple pulmonary emboli can have chronic pulmonary hypertension.

Arterial Emboli

An arterial embolus is a thromboembolism usually arising from mural thrombus.

Arterial emboli often cause infarction involving the brain (branches of the carotid artery), kidney (branches of the renal artery), and the intestine (branches of the mesenteric artery). Other sites affected include the spleen and lower extremities.

FLASH BACK

The three congenital heart defects that do not cause cyanosis:
AS**D**
VS**D**
PD**A**

Paradoxical Emboli

Paradoxical emboli are venous emboli that cross over from the right side of the heart to the left side and access systemic circulation. Most common co-existing defects are ASDs or a patent foramen ovale (PFO).

Fat Emboli

Bone marrow particles and fatty tissue travel to the lungs, brain, and kidney following severe long bone fractures (occurs 24–48 hours post-trauma). Patients present with petechiae, neurologic abnormalities, and pulmonary distress.

Gas Emboli

Caused by the introduction of air into the circulation; this is often seen in deep-sea divers who ascend from depth too rapidly. Nitrogen bubbles precipitate and block circulation, causing musculoskeletal pain also known as "the bends."

Amniotic Fluid Emboli

A complication of labor in which amniotic fluid leaks into maternal circulation following of maternal–fetal mixing, most commonly after trauma or placenta abruptio. Complications include disseminated intravascular coagulation (80%) and death (20%–90%).

SHOCK

Shock is a state of generalized hypoperfusion of tissues and cells in which O_2 delivery cannot meet O_2 demand. Initially the injury is reversible; however, as the hypoperfusive state continues the injuries become permanent and lead to multiple organ dysfunction syndrome (MODS). MODS can follow any type of shock and frequently involves the lung, kidney, heart, and liver (see Tables 1-29 and 1-30).

KEY FACT

Septic shock mimics an arteriovenous fistula (a high-flow state) because all arterioles are vasodilated, which leads to increased cardiac output.

Presentation

Patients usually present with tachycardia, oliguria, hypotension, weak pulses, mental status changes, and cool extremities.

Stages of Shock

- **Compensation:** Reflex mechanisms maintain perfusion of vital organs. These mechanisms include increased HR, increased peripheral resistance, release of catecholamines, and activation of the RAAS.
- **Decompensation:** Reflex mechanisms can no longer compensate, leading to tissue hypoperfusion, reversible tissue injury, and metabolic imbalance including metabolic acidosis and renal insufficiency.

TABLE 1-29. Types of Shock

Types of Shock	Pathophysiology	Clinical Examples	Treatment
Hypovolemic	Low circulating blood volume	Hemorrhage, burns, vomiting, diarrhea, severe dehydration	Replacement fluid and controlling fluid loss
Cardiogenic	Pump failure, often due to the LV	MI, arrhythmia, pulmonary embolism, cardiac tamponade	IV inotropic agents to increase cardiac output, arterial vasodilators to reduce resistance
Septic	Bacterial infection → endotoxin release → nitric oxide release, alternate complement pathway activation → polymorphonuclear leukocyte adherence to pulmonary capillaries → multiple organ dysfunction syndrome → tissue hypoxia	Gram-negative septicemia, disseminated intravascular coagulation	Fluid, vasopressors and antibiotics
Neurogenic	Severe trauma → loss of sympathetic nervous system signals → peripheral vasodilatation	Trauma involving spinal cord, brain stem, or cerebral injury	Fluid and vasopressors
Anaphylactic	Histamine release → increased venous capacitance	Type I hypersensitivity reaction	Epinephrine and securing the airway

Irreversible

Organ damage, organ failure, and irreversible tissue injury ultimately leading to death

Pathology

- Kidney: Acute tubular necrosis, oliguria
- Intestines: Mucosal ischemic necrosis and patchy hemorrhages, sepsis
- Brain: Necrosis
- Liver: Centrilobular necrosis ("shock liver")
- Adrenal: Waterhouse-Friderichsen syndrome of acute hemorrhagic infarction and adrenal insufficiency

TABLE 1-30. Hemodynamic Profile of Shock

Type of Shock	Cardiac Output	SVR	PCWP
Hypovolemic	↓	↑	↓
Cardiogenic	↓	↑	↑
Septic	↑	↓	↓
Anaphylactic	↑ or normal	↓	↓ or normal
Neurogenic	↓	↓	↓ or normal

KEY FACT

LAD infarction can cause LBBB, anterior wall rupture, and mural thrombi. RCA infarction can cause LV papillary rupture, posterior flail leaflet, and MR.

KEY FACT

Beck's triad of cardiac tamponade includes muffled heart sounds, elevated jugular venous pressure, and a fall in the systolic pressure.

KEY FACT

Pulsus paradoxus is a > 10-mmHg decline in systolic BP upon inspiration.

FLASH BACK

Parasternal pericardiocentesis requires the needle to pass through the skin, superficial and deep fascia, pectoralis major muscle, external intercostal membrane, internal intercostal membrane, transversus thoracis muscle, fibrous pericardium, and the parietal layer of the serous pericardium.

PERICARDIAL DISEASE

The pericardium is a double-layered sac that surrounds the heart, with the visceral pericardium lining the heart and the parietal pericardium on the outside. In between the two layers is pericardial fluid that helps to decrease friction.

Cardiac Tamponade

An increase of pericardial fluid that compresses the heart chambers, leading to impaired cardiac filling. The most common causes include neoplasms, postviral uremia, CHF, and hemorrhage either from trauma, ruptured LV following left anterior descending MI, active TB, or dissecting aortic aneurysm.

Presentation

Principal features include systemic venous congestion exhibited by jugular venous distention, peripheral edema and hepatomegaly, pulmonary venous congestion diagnosed through rales, and decreased cardiac output as evidenced by hypotension and tachycardia. Other features include elevated diastolic intracardiac pressure; a small, quiet heart with decreased heart sounds; and pulsus paradoxus.

Normally with inspiration the intrathoracic pressure becomes more negative, leading to increased venous return and increased filling of the right heart. This leads to intraventricular septal bulging into the LV, causing decreased cardiac output and BP. Any disease that causes high negative intrathoracic pressures or impaired right ventricular filling or outflow will exaggerate this mechanism, causing a > 10-mmHg decline in systolic BP upon inspiration (pulsus paradoxus).

Diagnosis

Echocardiography can help evaluate for pericardial effusion. In tamponade, there is collapse of the RA and RV during diastole. Definitive diagnosis is cardiac catheterization, which will show diastolic pressure equalization in all four chambers. ECG will show low voltage because the surrounding fluid will block the signal and cause electrical alternans, which is an alternate beat variation due to alteration of the position of the heart in relation to the recording electrodes as a result of an enlarged pericardial sac.

Treatment

Removal of fluid through pericardiocentesis

TABLE 1-31. Types of Pericarditis

Disease	Exudate	Associations
Serous	Protein-rich, straw-colored, few inflammatory cells	Associated with SLE, rheumatic fever, uremia, and viral infection (coxsackie B)
Fibrinous	Fibrin-rich with plasma proteins	Associated with MI, uremia, or rheumatic fever; can lead to scar formation and diastolic filling defects
Suppurative	Cloudy fluid with many inflammatory cells	Caused by bacterial infection leading to erythematous serosal surfaces
Hemorrhagic	Bloody and inflammatory fluid	Due to tumor invasion or TB

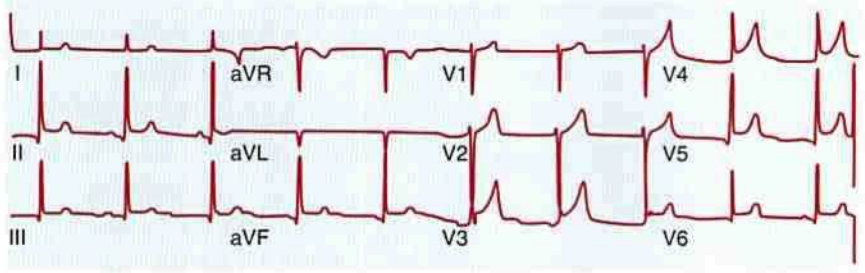


FIGURE 1-62. ECG findings in acute pericarditis. Notice the diffuse concave upward ST-segment elevation.

Acute Pericarditis

Inflammation of the Pericardium

There are three subtypes: serous, fibrinous, and hemorrhagic. These may resolve or lead to scarring and chronic adhesive or chronic constrictive pericarditis (see Table 1-31).

Presentation

Patients present with retrosternal chest pain (worse on inspiration or coughing; relief while sitting or leaning forward), fever, hypotension, jugular venous distention, pericardial friction rub, and distant heart sounds.

Diagnosis

Clinical suspicion with the presence of pleuritic and positional pain with a friction rub; ECG showing diffuse ST-segment elevation is often seen (see Figure 1-62).

Treatment

Treat the underlying etiology which includes NSAIDs for pain in viral pericarditis or Dressler's syndrome.

Chronic Constrictive Pericarditis

Gradual resorption of acute pericarditis can lead to fusion of the pericardial layers and scar formation with possible calcifications leading to a stiff pericardium. This results in inhibition of diastolic filling and signs similar to those of RHF may become evident. The most common cause worldwide is TB; however, it may also be secondary to pyogenic organisms or *Staphylococcus* spp. leading to obliteration of the pericardial cavity.

Presentation

Patients present with fatigue, dyspnea on exertion, hypotension and tachycardia due to decreased cardiac output and jugular venous distention, edema and ascites due to increased systemic venous pressure. Kussmaul's sign is also seen, in which the jugular veins distend during inspiration. Heart sounds are distant and a pericardial "knock" (early apical diastolic sound) is heard.

Diagnosis

Chest radiograph may show an enlarged cardiac silhouette, and CT or MRI may show pericardial thickening. Confirmation is by cardiac catheterization showing increased diastolic pressures.

KEY FACT

Scar tissue formation in acute pericarditis can often lead to constrictive pericarditis.

MNEMONIC

Causes of pericarditis–
CARDIAC RIND

Collagen vascular disease
Aortic aneurysm
Radiation
Drugs (hydralazine)
Infections
Acute renal failure
Cardiac Infarction
Rheumatic fever
Injury
Neoplasms
Dressler's syndrome

FLASH BACK

Dressler's syndrome is a delayed pericarditis that develops 2–10 weeks after an MI.

MNEMONIC

Pericardial **P**ain is **P**leuritic and **P**ositional.

KEY FACT

In contrast to an acute MI, in which ST-segment elevation is seen only in leads overlying the infarcted area, acute pericarditis is characterized by generalized ST-segment elevation.

TABLE 1-32. Acute Versus Chronic Pericardial Effusion

	Acute	Chronic
Etiology	Pericarditis, cardiac surgery, uremia, and collagen vascular disease	TB, cancer (lung, breast, or bone), SLE, HIV
Presentation	Chest pain, pericardial friction rub, pericardiocentesis reveals small amounts of fluid	With or without symptoms, large amounts of fluid on pericardiocentesis, symptom relief may or may not be seen after fluid is drained

Treatment

Effective treatment requires pericardial removal (pericardectomy).

Pericardial Effusion

Increased fluid accumulation sometimes occurs in the pericardial space. The volume of fluid, the rate of increase, and pericardial compliance all factor into the clinical symptoms of effusion. Can be acute or chronic (see Table 1-32).

Presentation

Usually asymptomatic, clinical features can include soft heart sounds, dullness over the posterior left lung and left-sided chest ache, or compressive symptoms such as dysphagia, hoarseness, or dyspnea.

Diagnosis

Echocardiography can quantify the volume of fluid in the pericardial sac. ECG will show low voltages and an increased cardiac silhouette will be seen on chest x-ray.

MNEMONIC

Konstrictive pericarditis presents with **K**ussmaul's sign and a pericardial **K**nock.

Treatment

Involves treatment of the underlying disorder or pericardiocentesis

PERIPHERAL VASCULAR DISEASE

Polyarteritis Nodosa (PAN)

A necrotizing immune complex inflammation and polymorphonuclear infiltration of the small to medium arteries that involves destruction of the media and internal elastic lamina. It most commonly affects middle-aged to older men, peaking at 50 years of age.

FLASH BACK

c-ANCA (cytoplasmic antineutrophil cytoplasmic antibody) is often associated with Wegener's granulomatosis.
p-ANCA (perinuclear antineutrophilic cytoplasmic antibody) is often seen in Churg-Strauss syndrome, microscopic polyangiitis, and primary sclerosing cholangitis.

Presentation

Symptoms are either inflammatory in nature such as fever and musculoskeletal pain, or due to decreased organ blood flow such as headache, abdominal pain, and hypertension. Ischemia of vessels can lead to distal disruption including **IHD**, **arthritis**, and **renal lesions**. There is **no lung involvement**. Hepatitis BsAg association is seen in 30% of those affected.

Diagnosis

Definitive diagnosis is by biopsy of the affected vessels. Antineutrophil cytoplasmic antibodies (ANCA) are highly suggestive of microscopic PAN.

Treatment

Immunosuppressives, prednisone

Temporal Arteritis

Also known as giant cell arteritis, temporal arteritis involves nodular inflammation, intimal fibrosis, and granulomas containing multinucleated giant cells in the medium to large arteries, most commonly of the carotid and aortic branches. Most often affects older women.

Presentation

Often affects the temporal artery, and symptoms include headache and sudden-onset visual defects, absence of pulse, facial pain, and jaw claudication. Ophthalmic artery involvement can lead to blindness. Patients can also have polymyalgia rheumatica, characterized by severe stiffness and aches in the axial skeleton (neck, shoulder girdle, and pelvic girdle).

Diagnosis

Definitive diagnosis is by biopsy of the affected vessel, usually the temporal artery, showing granulomatous inflammation. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein levels are also seen due to inflammation.

Treatment

First confirm elevated ESR, then immediately start high does of systemic steroids to prevent loss of vision while awaiting biopsy results.

Takayasu's Arteritis

Also known as pulseless disease, Takayasu's arteritis is an inflammation of the aorta and its branches usually affecting Asian women < 40 years old. It affects elastic arteries. (The most elastic arteries are the aorta and upper branching vessels.)

Presentation

Loss of the carotid, ulnar, and radial pulse leads to the distinctive "pulseless disease" designation. Inflammation of the affected vessels can lead to myocardial ischemia, hypertension, and visual defects. Systemic inflammatory effects such as fever, night sweats, arthralgia, and weight loss are also seen, most commonly in young Asian women.

Diagnosis

Angiography

Treatment

Steroids and cytotoxic drugs are used to reduce inflammation.

Thromboangiitis Obliterans

Also known as Buerger's disease, thromboangiitis obliterans is a full-thickness inflammation of the distal extremity medium-sized arteries, veins, and nerves. It is strongly associated with **young men** who are **heavy smokers**.

Presentation

Triad of distal arterial occlusion, Raynaud's phenomenon, and migrating superficial vein thrombophlebitis. May be so severe that it progresses to gangrene.



MNEMONIC

Takayasu's is aor**T**itis.
Kawasaki's: Picture Cows A Suckin' with their lips (mucocutaneous disease)



KEY FACT

Raynaud's phenomenon is when cold or stress exposure induces vasoconstriction of the digital arteries, causing the fingers/toes to turn white or blue. **Primary** Raynaud's phenomenon (Raynaud's disease) occurs in the absence of an underlying etiology, and is usually found in women, whereas **secondary** Raynaud's phenomenon is usually found in men with a **secondary** systemic disorder.

MNEMONIC

CHILD

Conjunctivitis
Hyperthermia (fever) > 5 days
Idiopathic polymorphic rash
Lymphadenopathy (cervical)
Dryness and redness (lips, mouth, palms, and soles)

KEY FACT

The triad of Wegener's is (1) focal necrotizing vasculitis, (2) necrotizing granulomas of the lungs and upper airway, and (3) necrotizing glomerulonephritis.

KEY FACT

Microscopic polyarteritis is a small-vessel vasculitis that is part of the Wegener's granulomatosis spectrum. It presents with similar symptoms, ANCA, and histologic findings as Wegener's, but without the respiratory findings.

FLASH BACK

The main side effect of **C**yclophosphamide is hemorrhagic **C**ystitis. Mesna is used to prevent cyclophosphamide-induced cystitis by binding to the metabolite acrolein in the bladder. Also, hydration helps to decrease drug time in the bladder.

KEY FACT

Cryoglobulinemic vasculitis is a small-vessel disease in which serum proteins precipitate out in the cold. Often due to hepatitis C, it is diagnosed with purpura, low complement, and immune deposits in vascular walls. Treatment involves plasmapheresis and hepatitis C treatment (interferon-alfa and ribavirin).

DIAGNOSIS

Arteriography may show distal stenotic corkscrew vessels. Definitive diagnosis involves tissue biopsy.

TREATMENT

Smoking cessation

Kawasaki's Disease

A mucocutaneous disease characterized by acute necrotizing inflammation of the small, medium, and larger arteries. It is often found in children younger than 4 years. The most serious sequelae include coronary vessel involvement, leading to aneurysms.

PRESENTATION

Symptoms include abrupt fever, rash, fissured lips, cervical lymphadenopathy, edema, **desquamation of hands and feet**, bilateral conjunctivitis, oral erythema, and development of coronary artery aneurysms.

DIAGNOSIS

Clinical diagnosis is made and coronary angiogram is performed to diagnose coronary artery aneurysms.

TREATMENT

Aspirin and γ globulin aid as anti-inflammatory agents. Long-term treatment in those with CAD includes aspirin and antiplatelet therapy. Anticoagulation is used in those with coronary aneurysms.

Wegener's Granulomatosis

A necrotizing granulomatous lesion affecting the small vessels in the kidney, lung, and upper respiratory tract.

PRESENTATION

- Renal: Red blood cell casts in the urine, proteinuria
- Pulmonary: Cough, nasal septum ulcers/perforation, sinusitis, dyspnea, hemoptysis
- Skin: Purpura

DIAGNOSIS

Ninety percent of patients are c-ANCA-positive, and definitive diagnosis is made through biopsy showing necrosis and granuloma formation. Chest x-ray shows nodular densities. Hematuria/red cell casts also aid in diagnosis.

TREATMENT

Prednisone, methotrexate, and cyclophosphamide.

Henoch-Schönlein Purpura (HSP)

A small-vessel IgA- and immune complex–mediated vasculitis that often follows upper respiratory infection in young children.

PRESENTATION

Symptoms include skin lesions that progress from blanching macules to petechiae to palpable purpura, often found on the **buttocks and legs** (nearly

pathognomonic). Patients can also complain of edema, polyarthritis, colicky abdominal pain, hematuria, and hypertension.

Diagnosis

Clinical diagnosis is made since laboratory tests are often normal.

Treatment

Supportive therapy and the use of corticosteroids for GI symptoms.

Churg-Strauss Syndrome

A small- to medium-sized granulomatous vasculitis associated with antibodies to neutrophil cytoplasmic antigens (p-ANCA).

Presentation

Patients present with asthma, cough, allergic rhinitis, arthralgias, and purpura. GI symptoms include bleeding, diarrhea, and colitis. Cardiac manifestations and peripheral neuropathy are also seen.

Diagnosis

Criteria include asthma, peripheral eosinophilia, paranasal sinusitis, pulmonary infiltrates, histologic proof of vasculitis, and polyneuropathy. Often p-ANCA-positive (70%).

Treatment

Supportive therapy and glucocorticoids.

KEY FACT

Platelet counts are often normal or elevated in HSP, whereas they are decreased in idiopathic thrombocytopenic purpura (ITP).

KEY FACT

When symptoms involve multiple organ systems and the patient presents with palpable purpura, think small-vessel vasculitis.

ISCHEMIC HEART DISEASE

IHD involves an interruption of arterial blood flow to the heart leading to an inadequate supply of O_2, often due to atherosclerotic narrowing of the coronary arteries. Risk factors include hypertension, family history, smoking, hypercholesterolemia (LDL > 160 mg/dL or HDL < 35 mg/dL), diabetes mellitus, age (male > 45 years old or female > 55 years old/postmenopausal), and tobacco use. IHD can present as angina pectoris, chronic IHD, or MI.

Angina Pectoris

Episodic chest pain caused by a disparity between cardiac perfusion and cardiac demand, leading to transient hypoxia of the myocardium.

Presentation

Typically presents as retrosternal chest pain or pressure that can radiate to the neck, jaw, or left arm, and lasts anywhere from 15 seconds to 15 minutes. Patients are often diaphoretic and nauseous. Precipitating factors include cold, food, and stress, whereas relieving factors include rest and nitroglycerin. There are three types: stable angina, unstable angina, and Prinzmetal's angina.

- **Stable angina:** The most common form in which pain is **induced by exertion** (usually the same amount of exertion causes pain); the pain is **relieved by rest** or nitroglycerin. Pain is thought to be due to **stenosis** of the atherosclerotic coronary arteries which can no longer supply enough O_2 to meet the increased demands of the heart during exertion. If pain occurs with exertion, the coronaries are generally > 70% stenotic; if pain occurs at rest, the arteries are > 90% stenotic.

TABLE 1-33. Drug Treatment for Stable Angina Pectoris

Drug	Reason for Use	Side Effects
Nitrates	Venous dilation to decrease preload, arteriolar dilatation to ↓ afterload, and coronary artery dilatation to ↑ O_2 supply	Orthostatic hypotension, reflex tachycardia, blushing, headache
β-Blockers	↓ sympathetic drive will ↓ myocardial O_2 demand and improve survival	Bronchoconstriction, insomnia
Calcium channel blockers	↓ preload and afterload	Hypotension, reflex tachycardia, flushing, headache

- **Unstable angina:** Pain at **rest** or with increasing frequency or duration during activity. Thought to be induced by a ruptured atherosclerotic plaque that leads to thrombosis and embolization. Unstable angina is more likely to lead to **MI** than is stable angina. Diagnosis is clinical with an angina-like presentation; however, no ST-segment elevations are seen on ECG. Treatment involves aspirin, nitrates, β-blockers and statins for lipid management. Heparin or glycoprotein IIb/IIIa inhibitors are also used. Patients are often sent for coronary angiography.
- **Prinzmetal's angina:** Also called variant angina, it presents as **intermittent chest pain at rest** that is not related to activity, stress, or BP. Often occurs during the night. It is thought to be due to **coronary artery vasospasm.** Cardiac catheterization may not demonstrate atherosclerosis and spasm can be precipitated with ergonovine. Definitive diagnosis involves exaggerated spasm of coronary arteries after injection with provocative agents such as ergonovine during coronary angiography. Treatment includes calcium channel blockers and nitrates.

Diagnosis

Many diagnostic modalities are available. ECG may show prior MI or ischemia. Stress tests may reveal inducible ischemia and coronary obstruction can be visualized on cardiac catheterization.

Treatment

Modification of risk factors is always helpful. Medical therapy for stable angina is shown in Table 1-33.

Surgical therapy includes coronary artery bypass graft and percutaneous transluminal coronary angioplasty.

KEY FACT

Cocaine can be a causative agent in MI by causing coronary vasospasm and thrombosis.

FLASH BACK

Atherosclerosis risk factors include hypertension, hypercholesterolemia, age, cigarette smoking, and diabetes.

MYOCARDIAL INFARCTION

MI is due to myocardial necrosis secondary to inadequate cardiac tissue perfusion. This leads to microscopic changes in the heart and release of myocardial enzymes into the bloodstream. Risk factors include increasing age, hypercoagulable states, vasculitis, and those that predispose to atherosclerosis.

Presentation

Patients will describe prolonged (> 30–45 minutes) crushing chest pain similar to angina, but **not relieved by nitroglycerin**, as well as nausea, vomiting, sweating, shortness of breath, and weakness. There are two patterns of myocardial involvement: Nontransmural and transmural (see Table 1-34).

TABLE 1-34. Gross and Microscopic Changes to the Heart in MI

Time	Gross Changes	Microscopic Changes
0–6 h	None	Vascular congestion, wavy monocyte fibers, contraction bands
12–24 h	Slight pallor, swelling, and softening	Start neutrophilic infiltration, **coagulation necrosis at 12 h**
1–7 d	Yellow pallor	Neutrophilic infiltrate replaced by macrophages on day 4
7–10 d	Yellow center softening surrounded by red border	Young fibroblastic growth and new vessel infiltration
10–28 d	Red connective tissue replacing yellow necrotic tissue	Continued phagocytosis, collagen synthesis
Months	Gray-white firm scar	Fibrous tissue replaces infarcted tissue that will not rupture because fibrosis adds to its strength

- **Non-ST-elevation myocardial infarct (NSTEMI):** Also known as non–Q wave MI. This is a MI that is limited to the inner one-half to one-third of the LV wall. Coronary artery atherosclerosis results in decreased coronary blood flow and loss of perfusion to the wall. **ST-segment depression** is seen on ECG.
- **ST-elevation myocardial infarct (STEMI):** This occurs following atherosclerotic plaque rupture and thrombosis leading to complete vessel occlusion (no blood flow!). Necrosis of the entire myocardial wall is seen. ECG is characterized by Q waves and **ST-segment elevation.**

Coronary artery thrombosis affects LAD > RCA > left circumflex coronary artery.

Diagnosis

ST-segment elevation is seen in transmural infarcts. ECG changes include:

- Tall peaked T waves starting immediately and lasting up to 1 day
- ST-segment elevation starting shortly after MI, due to injured myocytes
- Prolonged Q waves starting 1–4 days after MI, due to coagulative necrosis
- T-wave inversion starting within 1 day, signifying ischemia at the periphery of the infarct

Echocardiogram can show ventricular wall hypokinesia or akinesia.

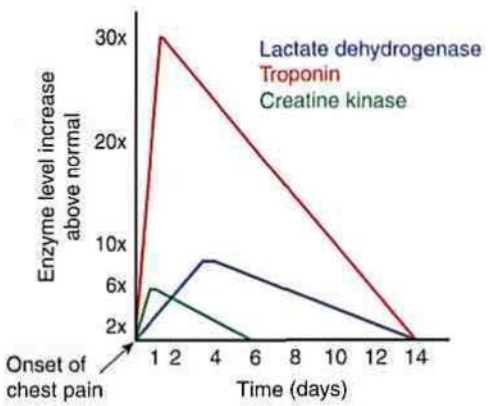


FIGURE 1-63. Cardiac enzyme changes with MI.

KEY FACT

Red infarcts occur in tissues with collateral circulation such as the lungs or intestines.

Pale infarcts occur in solid tissues with a single blood source such as brain, heart, and kidney.

CLINICAL CORRELATION

At 7–10 days there is an increased chance of ventricular aneurysms or rupture of the papillary wall due to the central softening.

When you see:	Think:
Coagulative necrosis	Ischemia of kidney or heart, pale tissue
Caseous necrosis	TB, cheesy appearance
Liquefaction necrosis	Tissue softening in brain or spinal cord
Fat necrosis	Trauma
Gangrenous necrosis	Foul-smelling black tissue, superinfection, limbs

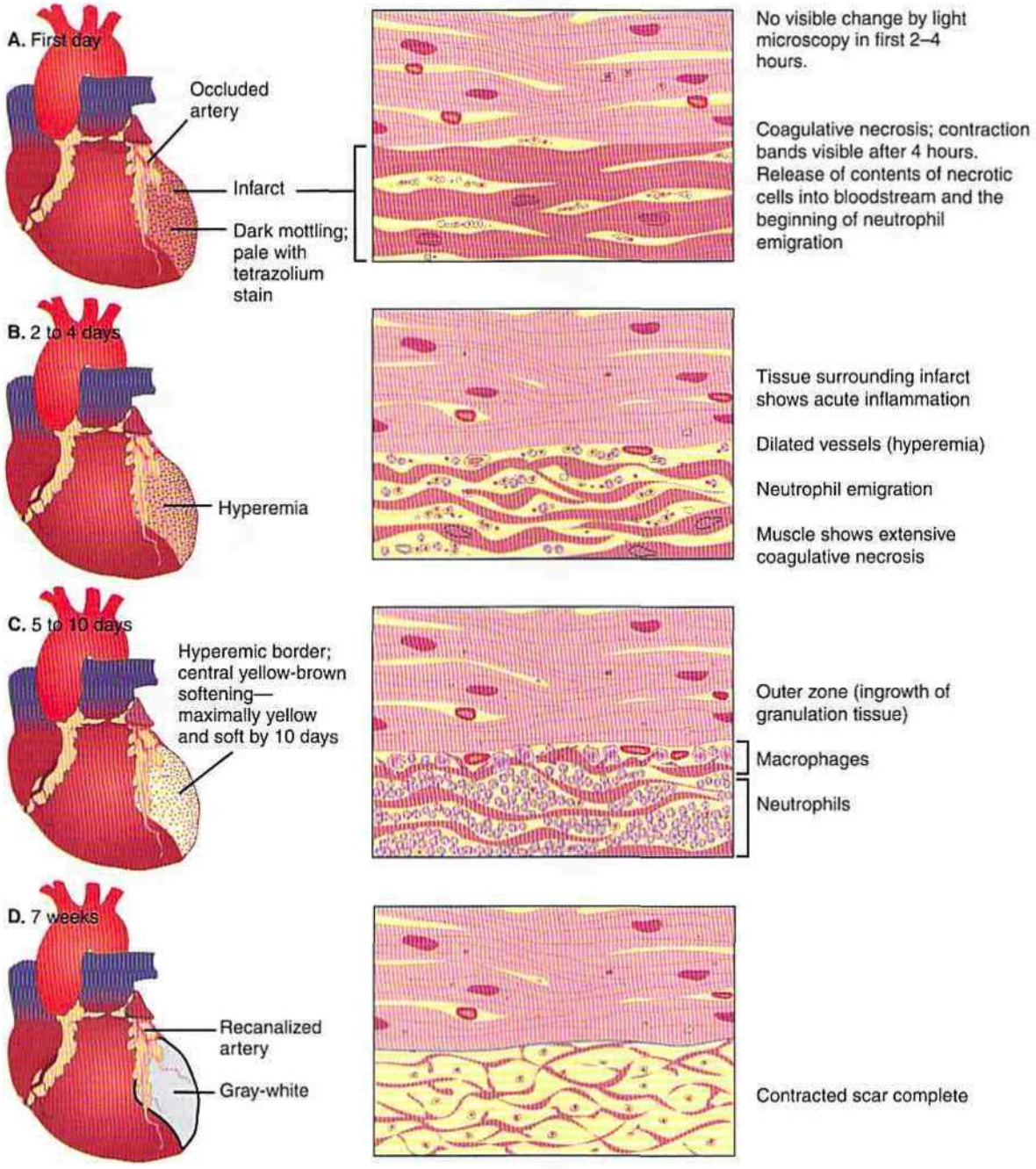


FIGURE 1-64. Evolution of MI. (Modified, with permission, from Chandrasoma P. *Pathology Notes*. South Norwalk, CT: Appleton & Lange, 1991: 224.)

Cardiac enzymes are widely used for diagnosis (see Figures 1-63 and 1-64).

- Troponin starts to elevate 4–6 hours after the pain starts and lasts 7–10 days. It is more specific than CK-MB.
- CK-MB is a specific enzyme for myocardial damage. Elevation starts 4–6 hours after the pain begins, peaks within 1 day, and lasts up to 3 days. It is the test of choice in the first 24 hours post-MI because if it disappears and a second spike occurs, this signals another MI is occurring (troponin would be elevated the entire time).
- Lactate dehydrogenase (LDH) is not used as frequently. It is elevated 12 hours after the pain starts and remains elevated for up to 2 weeks. Nor-

mally LDH-2 is greater than LDH-1, but in acute MI there is an "LDH 1-2 flip" and LDH-1 becomes elevated.
- Serum AST begins to increase after 12 hours and lasts from 3–5 days. It is nonspecific, as it can be found in liver, cardiac, and skeletal muscle.

Prognosis

- Arrhythmia is a common cause of death within hours of an MI.
- Sudden cardiac death.
- Heart block.
- Cardiogenic shock and CHF.
- Mural thrombus and systemic embolism.
- **Cardiac rupture**, resulting in cardiac tamponade, often ~7 days after an MI (LAD infarct most common).
- Posterior leaflet rupture (RCA).
- Aneurysm.
- **Pericarditis** is often seen 2–3 days post-MI but can occur later (at roughly 7 weeks = Dressler's syndrome).
- Silent MI occurs in the elderly diabetics who have a neuropathy that reduces sensory input.

Treatment

- Aspirin therapy: Anti-platelet therapy decreases post-MI mortality.
- Angioplasty is of more benefit than thrombolytics if it is readily available; however, if delayed its benefit is greatly reduced.
- Thrombolytics: Tissue plasminogen activator or streptokinase can be given within 12 hours unless contraindicated.
- β-Blockers have been shown to decrease mortality post-MI.
- Analgesics.
- Nitrates have no proven mortality benefit.
- Heparin.

CHRONIC ISCHEMIC HEART DISEASE (CIHD)

Ischemic heart damage causes CHF that can lead to CIHD. Often found in the elderly, infarction leads to cardiac hypertrophy and decompensation. No history of angina is typically present.

Imaging

RADIOGRAPHY

- X-ray penetration is inversely proportional to tissue density. Less x-ray absorption leads to a blacker image. Therefore, air is seen as black, while bone or metal is seen as white.
- Posteroanterior view describes the direction of the beam. The x-rays are transmitted from behind the patient onto a film placed anterior to the patient's chest.
- The normal cardiac silhouette occupies ≤ 50% of the width of the thorax.
- Increased pulmonary vasculature can be a sign of heart failure.
- It is imperative to be able to visualize both heart borders, as infection can blur the border lines.

MNEMONIC

To remember when the enzymes peak:

1/2 T-CAL 123:

Troponin: day 0.5
CK-MB: day **1**
AST: day **2**
LDH: day **3**

KEY FACT

Pericarditis presents with a friction rub on auscultation.

KEY FACT

Use angioplasty if available immediately; if not, use thrombolytics.

FLASH BACK

Red infarcts are seen in tissues with collateral circulation such as the lungs or intestines.
Pale infarcts are more often seen in solid tissues that have a single blood source, such as brain, heart, or kidney.

ECHOCARDIOGRAPHY

- A safe, noninvasive imaging modality using ultrasound.
- Can be used with Doppler to help evaluate blood flow, direction, turbulence, and estimation of pressure gradients.
- Can be transthoracic or transesophageal.
- Is used to evaluate fluid, ventricular function, valvular abnormalities, pericardial disease, cardiomyopathies, or CAD.

CARDIAC CATHETERIZATION

- Used for pressure measurement and contrast angiography.
- Right-sided pressures are normally measured by inserting a catheter through the femoral, brachial, or jugular vein, whereas left-sided pressures are measured through the brachial or femoral artery.
- Normal pressures are as follows:
  - RA: 0–8 mmHg
  - RV: 15–30/0–8 mmHg
  - Pulmonary artery: 15–30/4–12 mmHg
  - PCWP: 1–10 mmHg
  - LA: 1–10 mmHg
  - LV: 100–140/3–12 mmHg
  - Aorta: 100–140/60–90 mmHg

NUCLEAR IMAGING

- Used to evaluate myocardial perfusion and viability.
- Uses ^{99m}Tc-labeled compounds or ^{201}thallium.

STRESS TESTING

- Can be exercise or pharmacologic.
- In a nuclear stress test a patient is asked to exercise to maximum level and then a radioactive isotope (thallium or technetium) is injected into the bloodstream. The isotope will enter the coronary arteries that supply the myocardium. Any area that does not receive adequate blood supply will receive less isotope which will be seen on the images. Stress images are compared to resting images.
- If a patient is unable to exercise, dipyridamole or adenosine is given to increase cardiac blood flow.
- Abnormal results can signify CAD. The test can also be used for prognosis of patients post-MI and to determine the causes of chest pain in low-risk patients.
- Contraindications include acute MI within 2 days, severe aortic stenosis, acute myocarditis/pericarditis, acute pulmonary embolus, or acute aortic dissection.

PERICARDIOCENTESIS

- More than 20–30 mL of fluid accumulation in the pericardial sac is usually abnormal. A change in the cardiac silhouette is seen when > 250 mL of fluid accumulates.
- Indications include pericardial tamponade, symptomatic pericardial effusion, to obtain pericardial biopsy, and possible purulent pericarditis.

- Parasternal pericardiocentesis (the more common procedure) requires the needle to pass through the skin, superficial and deep fascia, pectoralis major muscle, external intercostal membrane, internal intercostal membrane, transversus thoracis muscle, fibrous pericardium, and the parietal layer of the serous pericardium.
- Subcostal pericardiocentesis requires the needle to pass through skin, superficial fascia, deep fascia, outer layer of the rectus sheath, rectus abdominis muscle, posterior layer of the rectus sheath, fibers of the diaphragm at its attachment to the costal margin, endothoracic fascia of the diaphragm, fibrous pericardium, and serous parietal pericardium.

Pharmacology

ANTIHYPERTENSIVE AGENTS

Hypertension is a common and serious disease with many sequelae, including MI, stroke, systemic vascular disease, and renal disease. Several classes of drugs are used to treat hypertension.

Diuretics

Diuretics act on the kidney with the primary purpose of reducing blood volume by increasing the rate of urine excretion. Reduction of blood volume leads to a decrease in BP. There are several types of diuretics, and they can be divided into separate classes based on their mechanism and site of action. Figure 1-65 serves as a review of the major diuretics.

Osmotic Diuretics (e.g., Mannitol)

Mechanism. **Increase kidney tubular fluid osmolarity.** The drug is filtered through the glomerulus into the kidney tubule. It cannot be reabsorbed, so it pulls water from the interstitial space into the tubules via osmosis. This process results in **more water being excreted** into the urine and less water being reabsorbed into the circulation.

Site of Action. In the kidney at the proximal tubule (site of major water permeability) (see Figure 1-66).

Uses. Rarely used for hypertension. More commonly used for patients with increased intracranial pressure (ICP) or increased intraocular pressure (IOP).

Side Effects. Can cause major problems if the drug cannot be filtered through the glomerulus (e.g., in anuria). In this situation, the drug remains in the circulation and pulls water from the interstitial tissues into the blood. This results in increased blood volume (the exact opposite of its intended effect), leading to peripheral and/or pulmonary edema.

Carbonic Anhydrase Inhibitors (e.g., Acetazolamide)

Mechanism. Prevent the conversion of HCO_3^- into CO_2 (mediated by carbonic anhydrase primarily at the brush border of proximal tubule cells), which is necessary for the reabsorption of HCO_3^-. This inhibition results in **excretion of HCO_3^- along with water** into the urine.

Site of Action. In the kidney at the proximal convoluted tubule (see Figure 1-66).

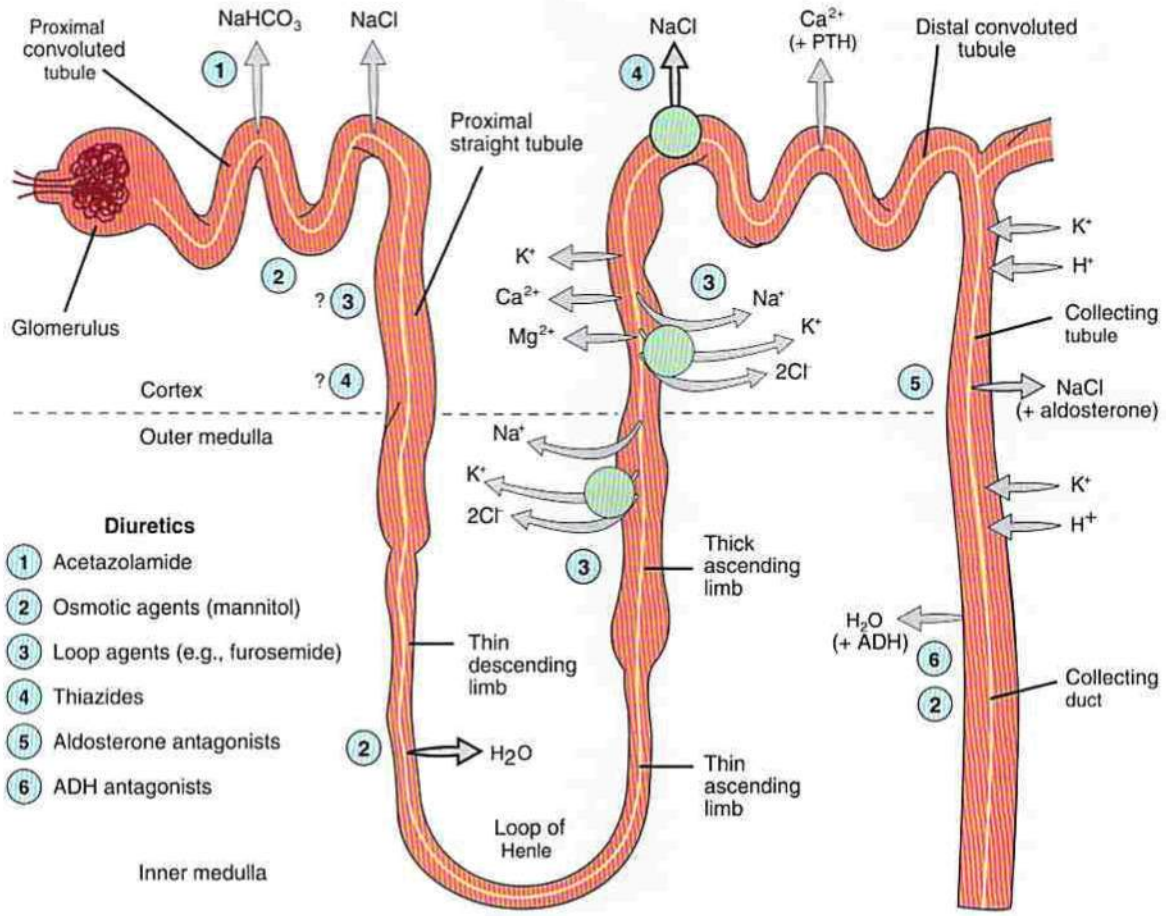


FIGURE 1-65. Overview of sites of action of various diuretics. (Modified, with permission, from Katzung BG, *Basic and Clinical Pharmacology*, 10th ed, New York: McGraw-Hill, 2007: 237.)

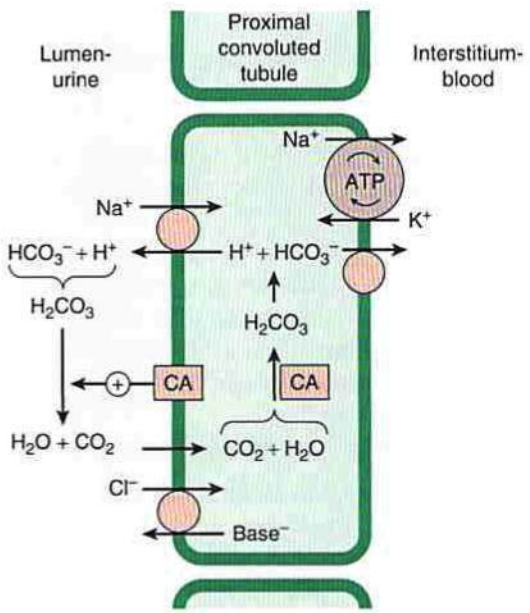


FIGURE 1-66. Ion physiology at the proximal convoluted tubule. (Modified, with permission, from Katzung BG, *Basic and Clinical Pharmacology*, 10th ed, New York: McGraw-Hill, 2007: 239.)

Uses. Rarely used for hypertension. More commonly used for patients with metabolic alkalosis, altitude sickness, glaucoma.

Side Effects. **Metabolic acidosis** due to increased excretion of HCO_3^-. The loss of this major source of alkalinity causes a rise in urinary pH and a drop in blood pH. In addition, acetazolamide contains a sulfa group, which causes allergic reactions in some patients.

MNEMONIC

ACIDazolamide causes **ACID**osis

Loop Diuretics (e.g., Furosemide, Ethacrynic Acid, Bumetanide)

Mechanism. **Inhibit Na^+-K^+-$2Cl^-$ channel** in the thick ascending limb of loop of Henle. By preventing Na^+ and K^+ reabsorption into the renal medulla, they abolish the hypertonicity of the medulla (so urine cannot be concentrated in the collecting ducts). This results in marked diuresis. They also **increase Ca^{2+} excretion** because they reduce the lumen positive potential in the loop of Henle (see Figure 1-67).

MNEMONIC

Loop Diuretics OH DANG!

Ototoxicity
Hypokalemia, **H**ypercalciuria
Dehydration
Allergy to sulfa (furosemide)
Nephritis
Gout

Site of Action. Thick ascending limb of loop of Henle (see Figure 1-67).

Uses. **The most efficacious diuretics**, used for edema (CHF, cirrhosis, nephrotic syndrome, and pulmonary edema), moderate to severe hypertension, and hypercalcemia.

Side Effects. Ototoxicity, **hypokalemia**, hypercalciuria, dehydration, allergy to sulfa (furosemide, not ethacrynic acid), nephritis, gout.

Thiazide Diuretics (e.g., Hydrochlorothiazide, Metolazone)

Mechanism. **Inhibit Na^+-Cl^- symporter**, thereby blocking Na^+ and Cl^- reabsorption in the distal convoluted tubule. NaCl is excreted along with water into the urine. They also increase Ca^{2+} reabsorption.

MNEMONIC

***Thiazides Hyper*GLUC**

Hyper**G**lycemia
Hyper**L**ipidemia
Hyper**U**ricemia
Hyper**C**alcemia

Site of Action. Early distal convoluted tubule (see Figure 1-68).

Uses. Mild to moderate hypertension, mild CHF, nephrogenic diabetes insipidus, idiopathic hypercalciuria.

Side Effects. Hyperglycemia, hyperlipidemia, hyperuricemia, hypercalcemia, sulfa allergy (hydrochlorothiazide).

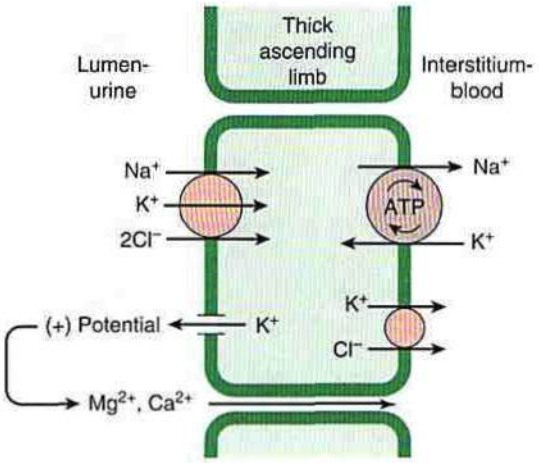


FIGURE 1-67. Ion physiology at the loop of Henle. (Modified, with permission, from Katzung BG, *Basic and Clinical Pharmacology*, 10th ed, New York: McGraw-Hill, 2007: 239.)

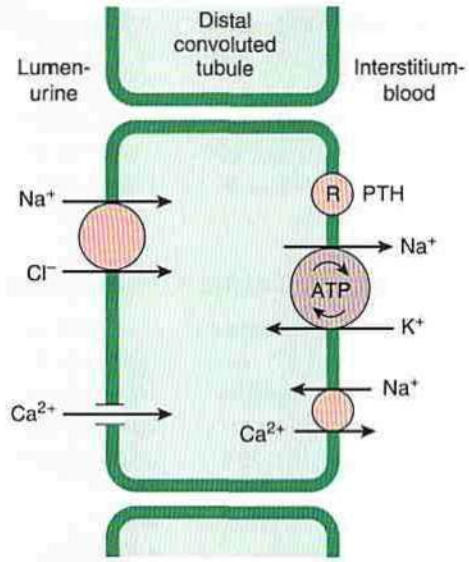


FIGURE 1-68. Ion physiology at the distal convoluted tubule. (Modified, with permission, from Katzung BG, *Basic and Clinical Pharmacology*, 10th ed, New York: McGraw-Hill, 2007: 239.)

MNEMONIC

The K+ STAys

Spironolactone
Triamterene
Amiloride

POTASSIUM-SPARING DIURETICS (E.G., SPIRONOLACTONE, TRIAMTERENE, AMILORIDE)

MECHANISM

- Spironolactone: Competitive antagonist at the aldosterone receptor in collecting tubule (indirectly inhibits Na^+ reabsorption).
- Triamterene and amiloride: Directly block Na^+ channels in the collecting tubule.

Reasons for the K-sparing properties of this class:

- Less K^+ secretion occurs due to inhibition of Na^+ reabsorption in the distal tubule (Na^+ reabsorption and K^+ secretion are coupled in this segment of the nephron).
- Because they are not active in the proximal portions of the tubules, these agents do not greatly increase tubular flow (high flow rates through the tubules increase secretion of K^+).

SITE OF ACTION. Collecting tubule and collecting duct (see Figure 1-69).

USES. Primarily used in combination with more efficacious diuretics (such as loop diuretics) to **prevent associated K^+ wasting**. Spironolactone has been proven to increase survival in patients with CHF.

SIDE EFFECTS. Hyperkalemia, spironolactone causes gynecomastia.

ELECTROLYTE CHANGES ASSOCIATED WITH DIURETIC USE. All diuretics affect the reabsorption and/or secretion of various electrolytes in the kidney, so electrolyte abnormalities may accompany the use of these drugs. See Table 1-35 for a review of some alterations in electrolytes in the urine and blood for various diuretics.

KEY FACT

BP = cardiac output × SVR.
Cardiac output = HR × SV.
SV depends on preload and heart contractility.

Sympathoplegics

FUNCTION OF SYMPATHETIC RECEPTORS

Sympathoplegic drugs reduce the effects of the SNS on the CV system (see Figure 1-70). Recall that arterial BP = cardiac output × systemic vascular resistance (SVR). Cardiac output is the product of HR and SV.

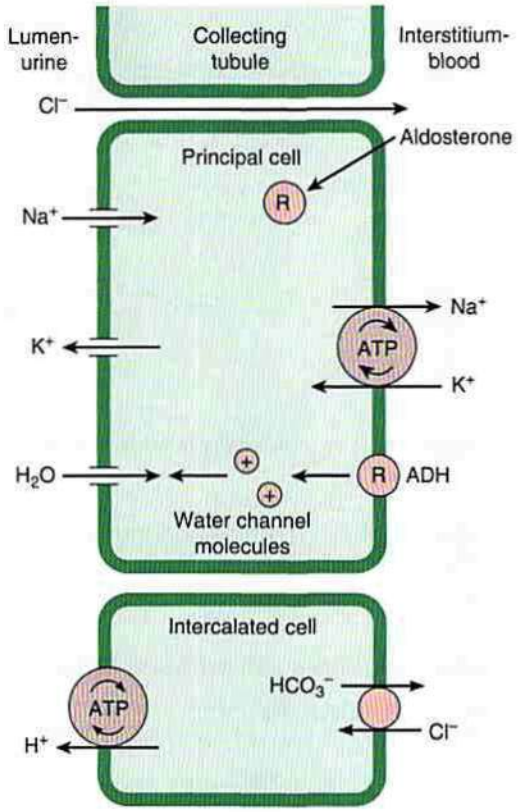


FIGURE 1-69. Ion physiology at the collecting tubule and collecting duct. (Modified, with permission, from Katzung BG, *Basic and Clinical Pharmacology*, 10th ed, New York: McGraw-Hill, 2007: 240.)

Since multiple factors contribute to BP control, pharmacologic agents that target different parameters can be used to decrease BP.

Sympathetic activity increases BP by increasing all of the following:

- HR
- Cardiac contractility
- Venous return to the heart (preload)
- SVR (or afterload)
- Renin production in the juxtaglomerular cells of the kidney

TABLE 1-35. Electrolyte Changes with Various Diuretics

Drug	Urine NaCl	Urine K^+	Urine Ca^+	Urine HCO_3^-	Blood pH
Osmotic diuretics	↑↑	↑	↑	↑	NC
Carbonic anhydrase inhibitors	↑	↑↑	NC	↑↑	↓
Loop diuretics	↑↑↑	↑↑	↑↑	NC	↑
Thiazide diuretics	↑	↑↑		NC	↑
Potassium-sparing diuretics	↑	↓	NC	NC	↓

NC = no change.

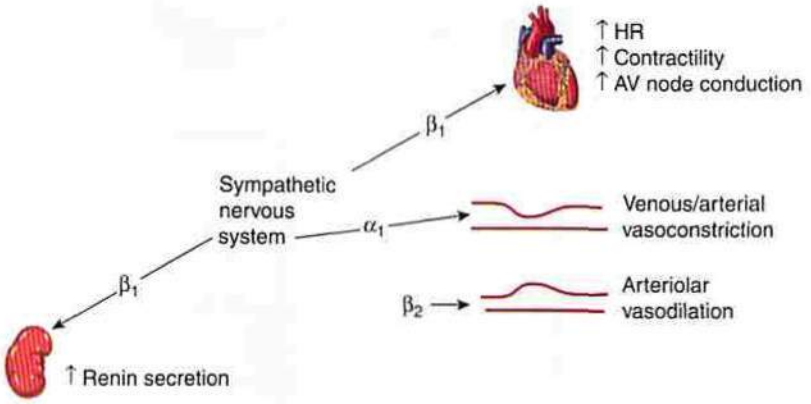


FIGURE 1-70. End-organ effects of SNS activity relating to BP control.

Drugs that inhibit sympathetic activity reduce some or all of these parameters and thus lower BP. (Review the major functions of the sympathetic receptor subtypes in Table 1-36.)

MNEMONIC

Methyldopa and **C**lonidine act **M**ainly **C**entrally.

CENTRALLY ACTING SYMPATHOPLEGICS (E.G., METHYLDOPA, CLONIDINE)

MECHANISM. **Selective α_2 agonists.** By activating α_2 receptors in the brain stem, these agents reduce central sympathetic outflow. The result is decreased cardiac output and SVR.

SITE OF ACTION. Brain stem.

KEY FACT

Methyldopa is the drug of choice to lower BP in pregnant patients.

USES. Rarely used for hypertension due to poor side-effect profile, but methyldopa is traditionally considered the drug of choice for hypertension in pregnant patients.

SIDE EFFECTS

- Methyldopa: Sedation, **positive Coombs' test** in 10% of patients (reversible upon discontinuation of drug).
- Clonidine: Sedation, dry mouth, **severe rebound hypertension** with abrupt discontinuation (should not use in patients who may have difficulty obtaining/taking medication as directed).

TABLE 1-36. Function of Sympathetic Receptors within the CV System

RECEPTOR	MAJOR EFFECTS ON CV SYSTEM
α_1	Vasoconstriction
α_2	▪ Central receptors: decrease sympathetic outflow ▪ Peripheral receptors: vasoconstriction
β_1	Increase heart rate, increase cardiac contractility, increase renin release
β_2	Vasodilation

α-Adrenergic Receptor Antagonists (α-Blockers; e.g., Prazosin, Doxazosin, Terazosin)

Mechanism. Selective α_1 receptor antagonists; α_1 blockade decreases SVR by preventing arteriolar vasoconstriction. The result is decreased BP.

Site of Action. Primarily α_1 receptors on arterioles. Of note, also blocks α_1 receptors at the bladder sphincter (see below for clinical uses).

Uses. Mild to moderate hypertension. Most common use of α_1 blockers is to treat urinary hesitancy for patients with prostatic hypertrophy (by preventing bladder sphincter contraction).

Side Effects. First-dose hypotension, reflex tachycardia, secondary Na^+ retention in kidney (use in combination with diuretic).

Remember, BP =Cardiac output× SVR. Therefore, increased SVR leads to increased BP.

MNEMONIC

α-Blockers end in **–OSIN.**

β-Adrenergic Receptor Antagonists (β-Blockers; e.g., Propranolol, Atenolol, Metoprolol, Esmolol, Carvedilol)

Mechanism

- Nonselective β receptor (β_1 and β_2) antagonists (propranolol):
  - Reduce HR by blocking β_1 effects
  - Reduce contractility by blocking β_1 effects
  - Inhibit renin production by blocking β_1 effects
  - More side effects because of their action on β_2 receptors (see side effects section)
- Selective β_1-receptor antagonists (atenolol, metoprolol, esmolol):
  - Same as above due to β_1 blockade
  - Fewer side effects
- Mixed α- and β-receptor antagonists (carvedilol):
  - Same as above due to β_1 blockade
  - Plus decreased SVR due to α blockade

MNEMONIC

Drugs with β-blocking action end in **–OLOL.**

Drugs with both α- and β-blocking action end in either **–ILOL** or **–ALOL.**

Site of Action. β_1 receptors on heart and kidney, β_2 receptors on arterioles

Uses. **Hypertension, angina, patients with previous MI, CHF.** Esmolol is an ultra-short-acting agent used in acute hypertensive emergencies.

Side Effects

- **Bradycardia:** Important to remember when checking vital signs on patients who are taking β blockers.
- **Bronchoconstriction** and asthma exacerbation (especially nonselective agents with β_2 antagonism).
- Blunted response to hypoglycemia. May be especially **dangerous in diabetics** on insulin therapy. Hypoglycemic episodes are marked by pallor, trembling, diaphoresis, and tachycardia (all mediated by increased β-receptor activity). With β blockade, these important clues of hypoglycemia may be absent.

KEY FACT

β_2 receptors in the lung mediate bronchodilation. β_2 blockade can impair breathing in patients with asthma or COPD.

Calcium Channel Blockers and Other Vasodilators

Vasodilators **decrease SVR** by relaxing smooth muscle in arteriole walls through a number of different mechanisms. The result is the same, however—by increasing arteriolar diameter, SVR (also known as afterload) is reduced, which also reduces BP (remember, BP = cardiac output × SVR).

Calcium Channel Blockers (e.g., Nifedipine, Amlodipine, Verapamil, Diltiazem)

Mechanism. Block L-type Ca^{2+} channels, inhibiting entry of Ca^{2+} into arteriolar smooth muscle; this action results in arteriole dilation and reduced SVR.

KEY FACT

Dihydropyridines are more active at the arterioles than the heart. Their names end in –PINE.

Site of Action

- **Vasoselective agents** work predominantly at the arteriolar smooth muscle. The most commonly used class is the **dihydropyridines** (including nifedipine and amlodipine).
- **Nonselective agents** act equally on the heart and the arterioles. Their vasodilating action is not as potent as that of the dihydropyridines, but they also reduce cardiac contractility. Examples are **verapamil** and **diltiazem**.

Uses. Mild to moderate hypertension.

Side Effects. Constipation, bradycardia, AV block.

Nitric Oxide Releasers (e.g., Nitroprusside)

Mechanism. Spontaneously releases nitric oxide, causing relaxation of arteriolar smooth muscle. This action results in rapid reduction of SVR and BP.

KEY FACT

Nitroprusside is a rapid-acting IV vasodilator for hypertensive emergencies.

Site of Action. Arteriolar smooth muscle.

Uses. Hypertensive emergencies (given in IV form).

Side Effects. By-products of metabolism include cyanide and thiocyanate, which can be harmful to patients with poor renal function. Other side effects include excessive hypotension and reflex tachycardia.

Other Vasodilators (e.g., Hydralazine, Minoxidil)

Hydralazine

Mechanism. Exact mechanism unknown.

Site of Action. Arteriolar smooth muscle.

Uses. Mild to moderate hypertension.

Side Effects. May cause **drug-induced lupus**; reflex tachycardia and sodium retention (therefore, it is given in combination with a β-blocker and a diuretic).

Minoxidil

Mechanism. Opens K^+ channels, causing hyperpolarization of smooth muscle cells and arteriolar dilation.

Site of Action. Arteriolar smooth muscle.

KEY FACT

Hirsutism means excessive hairiness.

Uses. Mild to moderate hypertension and baldness (see below).

Side Effects. **Hirsutism** (causing it to be used in a preparation called Rogaine for hair regrowth); also reflex tachycardia and sodium retention (also given in combination with β-blocker and a diuretic).

Angiotensin Inhibitors

The RAAS plays an intricate role in BP regulation. Two classes of drugs are used to alter this system and thereby reduce BP. Both classes reduce the action

of angiotensin II, which is a molecule that increases SVR by directly causing vasoconstriction. Angiotensin II also increases Na^+ and water reabsorption in the kidney (via aldosterone). The RAAS is shown in Figure 1-71.

Angiotensin-Converting Enzyme (ACE) Inhibitors (e.g., Captopril, Lisinopril, Enalapril)

Mechanism. These drugs **block ACEs**, thus preventing conversion of angiotensin II to angiotensin I. They also inhibit bradykinin (an intrinsic vasodilator) degradation. This action results in **decreased SVR and decreased Na and water reabsorption (via reduced aldosterone)**.

Site of Action. The active site of the enzyme (found on the endothelial membrane and in plasma).

Uses. **Mild to moderate hypertension, heart failure, diabetic renal disease.**

Side Effects. **Cough, hyperkalemia**, angioedema, proteinuria, taste changes, hypotension, fetal renal problems, rash.

Angiotensin II Receptor Antagonists (Also Called Angiotensin Receptor Blockers [ARBs]; e.g., Losartan, Valsartan)

Mechanism. Blockade of angiotensin II receptors, producing similar downstream effects as ACE inhibitors (namely, decreased SVR).

Site of Action. Heart, kidney, adrenal cortex.

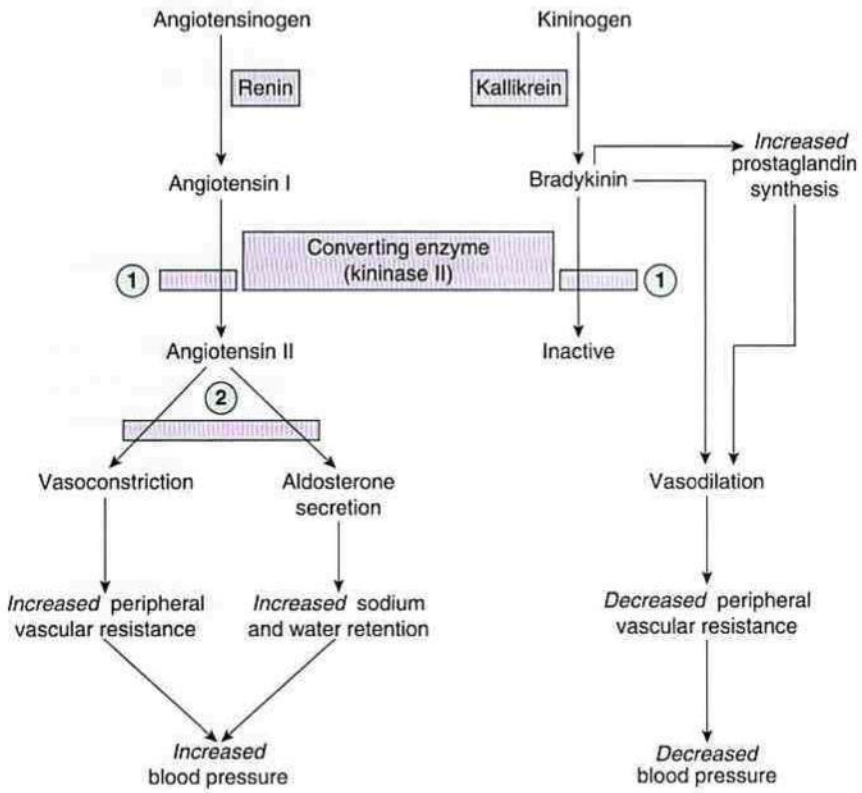


FIGURE 1-71. Renin-angiotensin-aldosterone pathway and sites of action of ACE inhibitors and angiotensin receptor blockers. 1 = ACE inhibitors; 2 = angiotensin receptor blockers. (Reproduced, with permission, from Katzung BG, *Basic and Clinical Pharmacology*, 10th ed, New York: McGraw-Hill, 2007: 176.)

MNEMONIC

All ACE inhibitors end in –PRIL.

KEY FACT

Angiotensin II is an enzyme responsible for aldosterone synthesis in the adrenal cortex and is also a direct vasodilator.

MNEMONIC

CAPTOPRIL

Cough
Angioedema
Proteinuria
Taste changes
hyp**O**tension
Pregnancy problems
Rash
Increased renin
Lower angiotensin II

MNEMONIC

All **ARBs** end in **–ARTAN.**

TABLE 1-37. Effects of ACE Inhibitors and Angiotensin Receptor Blockers

	ACE Inhibitors	ARBs
Renin	↑	↑
Angiotensin I	↑	↑
Angiotensin II	↓	↑
Aldosterone	↓	↓
Bradykinin	↑	↔

↑ = increases; ↓ = decreases; ↔ = no significant change.

Uses. Mainly used in patients who cannot tolerate ACE inhibitors.

Side Effects. **Less cough than ACE inhibitors**, fetal renal damage.

ACE inhibitors and ARBs affect levels of various products within the RAAS (see Figure 1-71 and Table 1-37).

ANTI-ANGINAL THERAPY

Angina is chest pain resulting from myocardial ischemia. Ischemia occurs when the demand of the heart exceeds the supply of the coronary arteries. Therefore, **reducing O_2 demand of the heart is the goal of treatment** so that supply is greater than demand. Some of the important factors that contribute to O_2 demand include **preload, afterload, HR, and cardiac contractility**. The major agents used to alter these parameters are nitrates, β-blockers, and calcium channel blockers. After reviewing the drugs, see Table 1-38 for a recap on how the drugs affect myocardial O_2 demand.

TABLE 1-38. Effects of Anti-anginal Agents on Parameters that Determine Myocardial O_2 Demand

Parameter	Nitrates	β-Blockers/Calcium Channel Blockers	Nitrate + β-Blocker/ Calcium Channel Blocker
Preload	↓	↑	↔
Afterload	↓	↓	↓
Contractility	↑ (reflex)	↓	↔
Heart rate	↑ (reflex)	↓	↓
O_2 demand	↓	↓	↓↓

↑ = increases; ↓ = decreases; ↔ = no significant change.

Types of Angina

There are three major forms of angina:

- Stable (effort) angina: Due to fixed narrowing of coronary arteries.
  - Occurs with increased activity
  - Is relieved by rest
- **Unstable angina:** Due to **acute formation of thrombus** on atherosclerotic plaque.
  - Not associated with activity
  - Is not relieved by rest
  - More likely to progress to MI
- **Variant (Prinzmetal's) angina:** Due to **coronary artery vasospasm.**

Nitrates (e.g., Nitroglycerin, Isosorbide Dinitrate)

Mechanism

Vasodilates via release of nitric oxide; major effect is **preload reduction** (veins dilate, blood pools in veins, and venous return to the heart decreases), resulting in decreased O_2 demand. May cause some afterload reduction also

Uses

Stable angina, unstable angina, and variant angina.

KEY FACT

Remember, nitroglycerin dilates **VEINS >> arteries.**

Side Effects

Tachycardia, orthostatic hypotension, headache.

β-Blockers (e.g., Metoprolol, Atenolol, Propranolol)

Mechanism

Reduce O_2 demand by reducing HR and cardiac contractility.

Uses

Stable angina, **not variant angina** (because β-blockade can disrupt the balance of α and β effects and worsen vasospasms).

Side Effects

Bradycardia, AV block.

Calcium Channel Blockers (e.g., Verapamil, Diltiazem, Nifedipine)

Mechanism

Decrease O_2 demand

- Verapamil, diltiazem: Decrease HR and contractility (like β-blockers)
- Nifedipine: Decreases afterload via vasodilation

Uses

Stable angina and variant angina (calcium channel blockers are the drugs of choice).

KEY FACT

Calcium channel blockers are the drugs of choice for variant (Prinzmetal's) angina.

Side Effects

Nifedipine may cause reflex tachycardia (increased O_2 demand); verapamil and diltiazem can cause constipation, bradycardia, and AV block.

DRUGS USED IN HEART FAILURE

Heart failure is defined as **cardiac output insufficient for the O_2 demands of the body**. It can be thought of as a chronic disease with intermittent acute exacerbations. Heart failure is characterized by poor cardiac output, and the response is to increase SNS tone and increase retention of sodium and water.

The goals of therapy are to increase cardiac output and also inhibit unwanted responses. Several drugs used in heart failure have been discussed previously. These include diuretics (e.g., furosemide, spironolactone), β-blockers (e.g., metoprolol, carvedilol), ACE inhibitors (e.g., captopril), ARBs (e.g., losartan), and vasodilators (e.g., nitroprusside, nitroglycerin). Review these drugs in the sections above and study Table 1-39 for their benefits in heart failure. Other drugs used to treat heart failure include agents that directly increase cardiac output such as β-agonists, cardiac glycosides, and phosphodiesterase inhibitors.

β-Agonists (e.g., Dobutamine)

Mechanism

Selective **β1-agonist**; this action increases HR and cardiac contractility, leading to an increase in cardiac output.

Site of Action

Primarily the heart.

Uses

Acute exacerbations of heart failure (given IV and has a very short half-life).

Side Effects

Angina (due to increased myocardial O_2 demand), tachycardia, arrhythmias.

TABLE 1-39. Drugs Used in the Treatment of Heart Failure

Drug Class	Examples	Benefits in Heart Failure
Diuretics	Furosemide, spironolactone	Reduced sodium/water retention → reduced preload and afterload; spironolactone prevents detrimental effects of aldosterone (myocardial fibrosis)
β-Blockers	Metoprolol, carvedilol	Reduced sympathetic tone → reduced afterload
ACE inhibitors/ARBs	Captopril, losartan	Reduced sympathetic tone → reduced afterload
Vasodilators	Nitroglycerin, nitroprusside	Vasodilation → reduced preload and reduced afterload
Cardiac glycosides	Digoxin	Increased cardiac contractility → increased cardiac output
β_1-Agonists	Dobutamine	Increased cardiac contractility → increased cardiac output
Phosphodiesterase inhibitors	Milrinone, inamrinone	Increased cardiac contractility → increased cardiac output

TABLE 1-40. Overview of Drugs Used to Treat Arrhythmias

Class	Example(s)	Mechanism	Clinical Use	Side Effects
I (Sodium channel blockers)				
IA	Quinidine, procainamide, disopyramide	Decrease ventricular conduction (increased QRS interval on ECG); prolong ventricular action potential **(increased QT interval on ECG)**	Atrial and ventricular arrhythmias	Quinidine: cinchonism (headache, tinnitus) and **torsades de pointes (due to increased QT interval);** procainamide: **drug-induced lupus**
IB	Lidocaine	Slow conduction and increased threshold for firing of abnormal cells	Acute ventricular arrhythmias	*CV and CNS depression* with overdose
IC	Flecainide, propafenone	Decrease ventricular conduction (increased QRS interval on ECG)	Ventricular arrhythmias	Can cause arrhythmias (especially in post–MI patients)
II (β-Blockers)	Esmolol (IV, rapid acting), metoprolol, propranolol	Decrease AV nodal conduction (increased PR interval on ECG)	Ventricular and supraventricular arrhythmias	Bradycardia, AV block
III (Potassium channel blockers)	Amiodarone, sotalol	Prolong ventricular action potential **(increased QT interval on ECG)**	Treatment and prevention of ventricular arrhythmias	Amiodarone: pulmonary fibrosis, hepatotoxicity, thyroid disease
IV (Calcium channel blockers)	Verapamil, diltiazem	Decrease AV nodal conduction	Supraventricular arrhythmias	Constipation, bradycardia, AV block
Other	Adenosine	Decrease AV nodal conduction	Supraventricular arrhythmias	Flushing, hypotension, chest pain
	Magnesium (Mg^{2+})	Unknown	Torsades de pointes	Respiratory depression

Cardiac Glycosides (e.g., Digoxin)

Mechanism

Blocks Na^+-K^+ ATPase, resulting in increased intracellular Na^+. The high levels of intracellular Na^+ reduce the activity of the Na^+–Ca^{2+} exchanger and more Ca^{2+} remains intracellular. This high level of intracellular Ca^{2+} **improves cardiac contractility** (leading to higher cardiac output). Digoxin also has some PS activity and **decreases AV nodal conduction velocity**.

Site of Action

Membrane of cardiac myocytes.

Uses

Chronic heart failure, also atrial fibrillation.

Side Effects

Arrhythmias, blurry yellow vision. Toxicities are highly **increased with hypokalemia** (important because many patients taking digoxin also take furosemide, a major cause of hypokalemia).

Phosphodiesterase Inhibitors (e.g., Inamrinone, Milrinone)

Mechanism

Block the action of phosphodiesterase, leading to increased levels of cAMP and increased Ca^{2+} flow into the cardiac myocyte. The result is increased cardiac contractility and cardiac output. Also cause some vasodilation.

Uses

Acute exacerbations of heart failure.

Side Effects

Arrhythmias.

ANTIARRHYTHMICS

Pharmacotherapy of arrhythmias is very complex (see Table 1-40).

LIPID-LOWERING AGENTS

Hyperlipidemia refers to increases in blood levels of lipoproteins and/or triglycerides. It is a major risk factor for CV diseases such as angina, MI, and stroke. Several pharmacologic agents are used to treat hyperlipidemia, and it is important to understand the key differences between the major classes of lipid-lowering agents (see Table 1-41 and Figure 1-72).

TABLE 1-41. Commonly Used Lipid-Lowering Agents

Drug Class	Example(s)	Mechanism	LDL	HDL	TGs	Side Effects
HMG-CoA reductase inhibitors ("statins")	Lovastatin, pravastatin, simvastatin, atorvastatin	Inhibit rate-determining step in cholesterol synthesis	↓↓↓	↑	↓	Increased LFTs, myositis
Bile acid resins	Cholestyramine, colestipol	Bind bile salts in the intestine thus preventing their reabsorption (along with cholesterol) in the intestine	↓↓	–	↑	Bad taste, bloating, constipation, impaired absorption of fat-soluble vitamins
Cholesterol absorption inhibitors	Ezetimibe	Block absorption of cholesterol in the small intestine	↓↓	–	–	Rarely increased LFTs
Fibrates	Gemfibrozil, fenofibrate, clofibrate	Increase synthesis of lipoprotein lipase via activation of peroxisome proliferator-activated receptor-α (PPAR-α)	↓	↑	↓↓↓	Myositis, increased LFTs
Other	Niacin (nicotinic acid, vitamin B_3)	Reduces secretion of VLDL resulting in less formation of LDL	↓↓	↑↑	↓	Flushed face (can be prevented by aspirin)

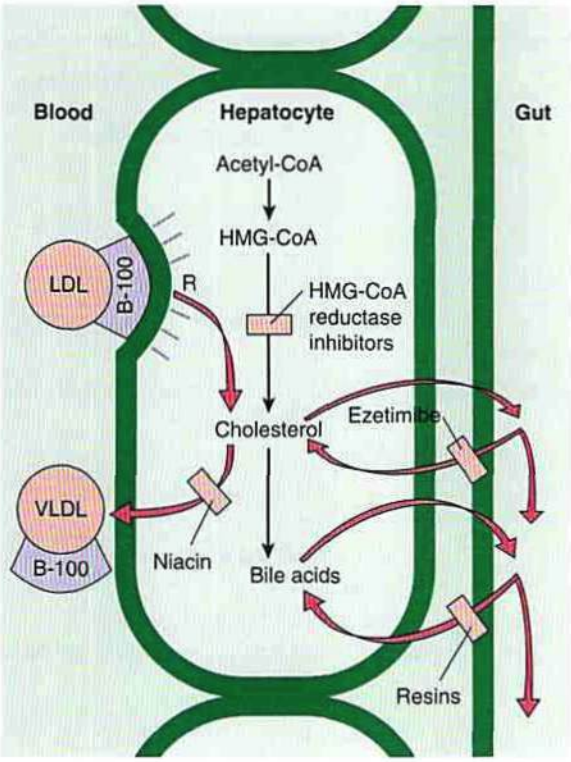


FIGURE 1-72. Overview of mechanisms of various lipid-lowering agents. (Modified, with permission, from Katzung BG, *Basic and Clinical Pharmacology*, 9th ed, New York: McGraw-Hill, 2004: 239.)

ANTICOAGULANTS

Anticoagulants are used for the treatment and prevention of unwanted blood clotting. Examples include DVT, PE, and embolic stroke. They prevent clot formation by interrupting either the intrinsic (heparin) or extrinsic (warfarin) coagulation cascade. It is very important to understand the similarities and differences of heparin and warfarin (see Table 1-42).

Heparin

Mechanism

Catalyzes the activation of antithrombin III, thus decreasing the activity of thrombin (factor IIa) and factor Xa. Heparin activity is monitored with the **partial thromboplastin time (PTT)** because of its effects on the **intrinsic coagulation pathway**. Newer low-molecular-weight heparins (e.g., enoxaparin) do not have to be monitored by laboratory tests.

Site of Action

Blood.

Uses

Immediate anticoagulation for DVT, PE, MI.

Side Effects

Bleeding. Action of heparin is reversed with **protamine sulfate** (binds heparin and inactivates it). Rarely causes heparin-induced thrombocytopenia (HIT).

TABLE 1-42. Comparison of Heparin and Warfarin

Drug	Heparin	Warfarin
Structure	Large anionic polymer	Small lipid-soluble molecule
Route of administration	IV, SC	Oral
Site of action	Blood	Liver
Onset of action	Rapid (seconds)	Slow, dependent on half-life of clotting factors.
Mechanism of action	Activates antithrombin III, reduces action of thrombin and Xa	Vitamin K antagonist (impairs synthesis of factors II, VII, IX, and X)
Duration of action	Acute (hours)	Chronic (weeks)
Treatment of overdose	Protamine	Fresh frozen plasma
Method of monitoring	PTT (intrinsic pathway)	PT (extrinsic pathway)



To remember that warfarin activity (affecting the extrinsic pathway) is measured with PT, think WEPT (Warfarin, Extrinsic, PT)

Warfarin

Mechanism

Inhibits γ carboxylation of vitamin K–dependent clotting factors (factors II, VII, IX, and X, and proteins C and S). Warfarin affects the **extrinsic coagulation pathway** and is monitored clinically with the **prothrombin time (PT)**.

Site of Action

Liver (site of synthesis of clotting factors).

Uses

Chronic anticoagulation (e.g., DVT prophylaxis and in atrial fibrillation for stroke prophylaxis).

Side Effects

Bleeding. Also, warfarin crosses the placenta, so it is **contraindicated in pregnancy** (heparin is used instead). Overdose is treated with fresh frozen plasma (to supply fresh clotting factors).

ANTIPLATELET AGENTS

Drugs that have antiplatelet activity either inhibit platelet adherence to the vascular endothelium (adhesion) or platelet adherence to other platelets (aggregation). There are several agents used currently. Their major applications are to prevent myocardial infarction and stroke (see Figure 1-73 for an overview of platelet activation).

Aspirin

Mechanism

Acetylates and irreversibly inhibits cyclooxygenase (COX-1 and COX-2). This action prevents conversion of arachidonic acid to prostaglandins and thromboxane A_2. The result is decreased platelet aggregation.

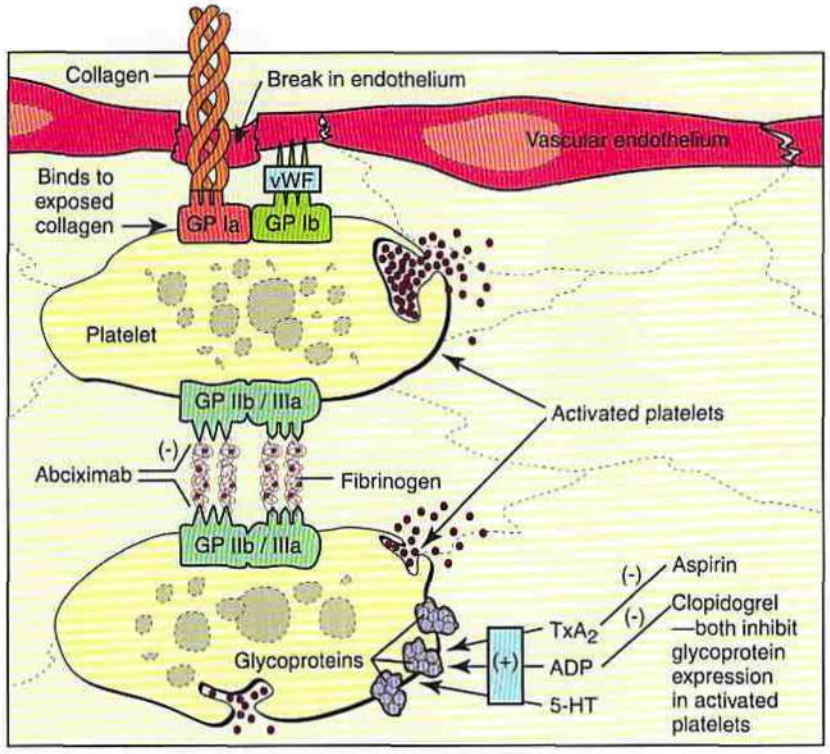


FIGURE 1-73. Factors influencing platelet activation.

Site of Action

In the platelet.

Uses

Prevention of MI.

Side Effects

Gastric ulcers, bleeding, Reye's syndrome in children, tinnitus at very high doses.

Clopidogrel and Ticlopidine

Mechanism

Irreversibly blocks ADP receptors on platelet membranes, thereby inhibiting platelet aggregation.

Site of Action

Platelet membrane.

Uses

Prevention of thrombosis following coronary artery stent placement; stroke prevention.

Side Effects

Bleeding. Ticlopidine can cause severe neutropenia.

Dipyridamole

Mechanism

Inhibits adenosine uptake by the platelet (secondary to blocking intra-platelet phosphodiesterase and increasing cAMP levels). The result is decreased platelet aggregation.

Site of Action

In the platelet.

Uses

In combination with aspirin to prevent stroke.

Side Effects

Bleeding.

Abciximab

Mechanism

Binds to glycoprotein IIb/IIIa receptor on platelets and prevents interaction between fibrinogen and IIb/IIIa receptor. The result is decreased platelet aggregation.

Site of Action

Platelet membrane.

Uses

Prevention of thrombosis during coronary artery angioplasty and stenting.

Side Effects

Bleeding, thrombocytopenia.

THROMBOLYTICS

Thrombolytics are used to lyse active clots in the circulation. Their basic mechanism is to increase formation of plasmin, the intrinsic enzyme responsible for degrading fibrin clots. The two most common applications for thrombolytic agents are early MI and early thromboembolic (ischemic) stroke.

Streptokinase

Mechanism

Indirectly activates plasminogen. Streptokinase first binds plasminogen, forming a 1:1 complex. This complex then catalyzes the formation of plasmin from another molecule of plasminogen. Streptokinase is **not fibrin-specific** (it activates free plasminogen that is not bound to fibrin clots).

Site of Action

Free plasminogen and fibrin-bound plasminogen.

Uses

Acute MI, stroke, PE.

Side Effects

Bleeding (contraindicated in patients with active bleeding, recent surgery, or history of intracranial bleeds); **allergic response** (since it is isolated from bacteria); it also loses efficacy after initial administration because patients become sensitized; a repeat dose is much less effective than the initial dose.

Tissue Plasminogen Activator (tPA)

Mechanism

In contrast to streptokinase, **tPA is fibrin-specific**. Therefore it only activates plasminogen molecules that are bound to fibrin clots. It directly activates plasminogen.

Site of Action

Plasminogen bound to fibrin clots.

Uses

Acute MI, stroke, PE.

Side Effects

Bleeding; does not lose efficacy after initial dose (in contrast to streptokinase).
Note: Fibrinolysis can be reversed with **aminocaproic acid**.

Rapid Review

Key Terms

Intima	The innermost concentric layer of vessel walls composed of a single layer of endothelial cells.
Internal elastic lamina	A dense elastic membrane separating the tunica intima and media.
Media	The middle layer of vessel walls composed of smooth muscle cells; it is supplied with O_2 and nutrients by diffusion from the lumen and by **vasa vasorum**.
External elastic lamina	The outer limit of the tunica media, separating it from adventitia.
Adventitia	The outer layer of vessels, consisting of connective tissue and the **vasa vasorum**.
Vasa vasorum	Small vessels outside medium and large vessels that provide nutrients to the media.
Internal elastic lamina	A dense elastic membrane separating the tunica intima and media.
Elastic arteries	Large arteries (the aorta, its larger branches, and the iliac) characterized by a thick media containing **elastin** (necessary for elastic rebound to handle high pressures).
Muscular arteries	Medium-sized arteries that comprise other branches of the aorta (coronary and renal), and are characterized by thick media containing mostly smooth muscle, which allows them to regulate blood flow to organs.

(continued)

Key Terms *(continued)*

Arterioles	The smallest arteries found within tissues, characterized by media only 1 or 2 smooth muscle cells thick, that function to regulate blood flow to capillary beds and act as principal points of physiologic resistance to blood flow.
Cardiac tamponade	Compression of the heart due to fluid accumulation within the pericardium, leading to decreased cardiac output. Symptoms include pulsus paradoxus, electrical alternans on ECG, and Beck's triad (hypotension, distant heart sounds, and JVD).
Pulsus paradoxus	A fall in systolic BP of > 10 mmHg with inspiration.
Metabolic syndrome	Abdominal obesity, elevated triglycerides, low HDL cholesterol, hypertension, insulin resistance, and prothrombotic/proinflammatory states.

HYPERTENSION

Defined as BP > 140/90 mmHg measured on two separate occasions (normal BP is < 120/90 mmHg). Long-term sequelae include LV hypertrophy, aortic dissection, stroke, CHF, CAD, and renal failure. Risk factors are age, obesity, diabetes, smoking, genetics, and race (black > white > Asian). Classified according to the following etiology:

- **Essential hypertension.** Accounts for 95% of hypertension and is due to an idiopathic (unknown) cause. Controllable and generally asymptomatic unless complications develop
- **Secondary hypertension.** Hypertension secondary to an identifiable cause, such as renal disease, primary aldosteronism, Cushing's syndrome, renal artery stenosis, or eclampsia.
- **Malignant hypertension.** Rapidly increasing BP (SBP > 200 mmHg) leading to death within 2 years if untreated. Small arteries become thickened and occluded, causing distal tissue ischemia, renal failure, retinal hemorrhages, and sometimes papilledema.

Hypertensive Vascular Disease

Hypertension has adverse effects on the vascular system, producing a series of stereotyped pathologic changes.

Benign Nephrosclerosis

A common small-blood-vessel disease associated with hypertension. Affects elderly and diabetic patients. Arteriolar narrowing impairs renal blood supply.

Hyaline Arteriolosclerosis

Characteristic vascular lesion of benign nephrosclerosis. Hyaline thickening of the arteriole walls, causing narrowing of the lumen. As a result, arterioles appear pink on histology.

Hyperplastic Arteriolosclerosis

Small blood vessel disease associated with acute or severe elevations of BP (malignant hypertension). Blood vessels have "onion skin" concentric thickening of the arteriolar walls with progressive lumen narrowing. In malignant hypertension, vessel walls also have necrotic deposits (necrotizing arteriolitis).

RENOVASCULAR HYPERTENSION

Form of secondary hypertension characterized by renal artery stenosis which decreases glomerular blood flow and pressure. The decreased pressure activates the RAAS, leading to increased BP.

Renin-Angiotensin System

Major endocrine regulatory system controlling BP via peripheral vascular resistance and sodium balance: Decreased renal blood flow causes increased secretion of renin. Renin cleaves angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II by ACE. Angiotensin II increases aldosterone secretion (acts to increase Na^+ reabsorption by the kidney). Water follows the Na^+, leading to increased body fluid volume and increased BP. Dysfunction of the system causes hypertension (hyperaldosteronism and Cushing's disease).

Fibromuscular Dysplasia (FMD)

A disease resulting in narrowing of small and medium-sized arteries (primarily renal arteries) leading to hypertension. Often affects young women.

ANEURYSMS

Abnormal dilation of a blood vessel.

- **True aneurysm.** Aneurysm affecting **all** arterial wall components
- **False (pseudo-)aneurysm.** A fibrous containment of blood that has leaked into surrounding tissues following disruption of the arterial wall; often occurs following penetrating trauma or catheterization

Abdominal Aortic Aneurysm (AAA)

Most common form of aneurysm. Typically affects men > 50 years old with **atherosclerosis** and occurs between the renal arteries and the aortic bifurcation. Classically presents as a palpable pulsating abdominal mass. They can become large, are filled with blood, and may result in **rupture** (with subsequent loss of massive amounts of blood into the peritoneal cavity), obstruction or compression of other structures, or **release of emboli** (resulting in stroke, MI).

TABLE 1-43. Other Less Common Causes of Aneurysms

Inflammatory	Caused by an inflammatory process of uncertain cause that weakens the wall of the aorta. It involves dense periaortic fibrosis containing abundant inflammatory cell infiltrate.
Mycotic	Caused by infection that weakens the wall of the abdominal aorta; due to complications of infective endocarditis, including release of septic emboli that lodge in vessel walls, adjacent suppurative processes spreading to the aorta, or circulating organisms directly infecting the arterial wall.
Syphilitic	Caused by tertiary syphilis. Inflammation begins with the vasa vasorum of the aorta, causing narrowing of their lumina, leading to ischemic injury of the aortic media. The destruction of media causes the aorta to lose its elastic recoil and it begins to dilate (syphilitic aneurysm). **Obliterative endarteritis** is the destructive inflammatory process of syphilitic aneurysms that destroy the vasa vasorum of the aorta, leading to ischemic injury.

TABLE 1-44. Classification of Aortic Dissection

Type I	Affects ascending and descending aorta.
Type II	Affects ascending aorta only.
Type III	Affects descending aorta only.

Marfan's Syndrome

Thoracic aortic aneurysm or dissection is commonly seen in this connective tissue disease (see Table 1-43).

Aortic Dissection

Formation of a blood-filled channel within the aortic wall due to tearing of the aortic intima (due to **cystic medial necrosis**). Blood pushes into the space and creates a pocket that expands down the aorta. The blood becomes trapped in the second, pseudo-lumen. Rupture may result in the release of the trapped blood, and can cause hypovolemic shock (the major cause of death in aortic dissection).

- **Hypertension.** Found in 95% of patients with aortic dissection
- **Connective tissue disease.** Increased incidence of aortic dissection is seen with **Marfan's syndrome** and **Ehlers-Danlos syndrome** (see Table 1-44).

ATHEROSCLEROSIS AND ARTERIOSCLEROSIS

Atherosclerosis

Deposition of fatty material in vessel walls. Accumulated material hardens into plaques that can eventually occlude the lumen. Complications include plaque rupture, ulceration, or erosion through the vessel, which can induce thrombus formation or emboli (increasing the risk of stroke and MI). Plaques weaken vessel walls, predisposing them to aneurysm formation (particularly aortic aneurysms).

Atheroma

Characteristic intimal lesions that protrude and obstruct vascular lumens and weaken vessel walls. Composed of a necrotic, soft yellow core of lipid (mainly cholesterol) covered by a fibrous cap. Develop from "fatty streaks" in large- to medium-sized muscular arteries (abdominal aorta > thoracic and major aortic branches)

Risk Factors for Atherosclerosis

Older age, male gender, family history, low physical activity, obesity, high stress, diabetes, cigarette smoking, and alcohol and saturated fat intake

Response to Injury Hypothesis

Theory describing the cause of atheroma formation. Endothelial injury allows adhesion of monocytes and platelets, then monocytes and smooth muscle cells migrate into the intima, and smooth muscle cells proliferate resulting in plaque formation.

Arteriosclerosis

Thickening and loss of elasticity (stiffening) of the arterial walls

Mönckeberg Medial Calcific Sclerosis

A form of arteriosclerosis affecting people > 50 years old. Characterized by calcific deposits in the **media** of muscular arteries. Calcification does not obstruct the vessel lumen. Seen on x-rays and may be palpable, depending on the affected vessel

Arteriolosclerosis

A form of arteriosclerosis affecting small arteries and arterioles. Causes downstream ischemic injury due to narrowed vessel lumens. Associated with hypertension and diabetes mellitus.

ARTERIOVENOUS FISTULA

Abnormal communication between arteries and veins. Arises from developmental defects, vascular injuries, or may be iatrogenic (fistulas made to allow vascular access for hemodialysis). Pathology occurs if the arteriovenous shunt causes the heart to pump too much blood, leading to **high-output cardiac failure**.

VENOUS DISEASE

Varicose Veins

Abnormally dilated and tortuous veins, predominantly seen in the lower extremity. Caused by increased intraluminal pressure with loss of vessels wall support and deformed valves. Increased incidence during pregnancy

Esophageal Varices

Dilatation of the lower esophageal veins due to cirrhosis of the liver. Rupture of these veins leads to massive upper GI hemorrhage.

Hemorrhoids

Varicose dilations of veins at the anorectal junction.

Migratory Thrombophlebitis (Trousseau's Syndrome)

Hypercoagulability secondary to malignancy resulting in venous thromboses appearing at one site, disappearing, and then reappearing in other veins. Occurs as a paraneoplastic syndrome (lung, pancreas, and colon).

Deep Vein Thrombosis

Thrombosis occurring in the deep veins (usually the leg veins). High risk of thrombus dislodging and becoming wedged in the pulmonary circulation leading to sudden death (PE).

- **Homans' sign.** Pain elicited upon forced dorsiflexion of the foot; due to thrombi in the legs. Bedridden patients may show no other signs of deep venous thrombi.

Hypercoagulable State

Caused by malignancy, hyperestrogenism, pregnancy, factor V Leiden mutation (most common cause of inherited hypercoagulability), protein C or S deficiency, antithrombin III deficiency, homocystinemia, fibrinolysis defects, prothrombin gene mutation, prolonged immobilization, and smoking.

Virchow's Triad

Hypercoagulable state, stasis, and vessel injury.

Superior Vena Cava Syndrome

Symptoms include cyanosis, sensation of facial/head fullness, and dilation of head, neck, and arm veins. Caused by neoplasms (bronchogenic carcinoma and mediastinal lymphomas) compressing or invading the SVC, leading to impaired drainage of the vessels above the level of the blockage. Often accompanied by respiratory distress (pulmonary venous compression).

Inferior Vena Cava Syndrome

Obstruction of the IVC presents with edema in the legs, distention of the superficial veins of the lower abdomen, and if renal veins are involved, massive proteinuria. Caused by neoplasms (liver and kidney cancers) or thrombi that compress or occlude the IVC.

LYMPHATIC DISEASE

Lymphangitis

Acute inflammation of the lymphatic channels due to systemic bacterial infection. The lymphatics become dilated and filled with an exudate that extends through the wall causing cellulitis and abscess formation. Painful subcutaneous red streaks (inflammation of the vessels) with an accompanying painful enlargement of lymph nodes can be seen.

Lymphedema

Obstruction of lymphatic drainage causing accumulation of interstitial fluid and dilation of the lymphatics up to the point of obstruction, edema, and a peau d'orange appearance of the skin. Subsequent rupture of the obstructed vessel can produce:

- **Chylous ascites.** Rupture into the peritoneum
- **Chylothorax.** Rupture into the pleural cavity
- **Chylopericardium.** Rupture into the pericardium

CONGESTIVE HEART FAILURE

Condition in which the heart is unable to eject the blood delivered to it, typically resulting in multiple systemic abnormalities affecting the lungs, liver, and kidneys. Results in increased end-diastolic volume, increased back pressure on the lungs (pulmonary hypertension and/or edema), and venous system congestion

- **Signs and symptoms.** Ankle edema, hepatomegaly, dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and proteinuria
- **Causes.** Hypertension, valvular disease, IHD, and primary myocardial disease (left-sided heart failure). Left-sided heart failure is the most common cause of right-sided failure.

Cor Pulmonale ("Pulmonary Heart Disease")

Right-sided heart failure due to pulmonary hypertension **not** caused by left-sided heart failure. Most commonly results from pulmonary vasculature or parenchymal disease, acute PE, or restrictive lung disease.

ISCHEMIC HEART DISEASE

The most common cause of IHD is narrowing of coronary arteries as a result of atherosclerosis (CAD).

Angina Pectoris

Chest pain that is typically crushing and substernal with radiation down the left arm. Accompanied by sweating, shortness of breath, nausea, and lightheadedness. Is a sign of ongoing ischemia or infarct. Can exist in three forms: stable, unstable, and variant (Prinzmetal's).

- **Stable angina.** Chest pain occurring with exertion and relieved by rest or nitrates; usually indicates > 75% stenosis
- **Variant (Prinzmetal's) angina.** Chest pain occurring at rest (including at night while lying in bed). Caused by coronary artery vasospasm
- **Unstable angina.** Chest pain occurring with increasing frequency precipitated by little exertion or even at rest. Pain is more intense and lasts longer. Unstable angina is a predictor of worsening CAD.

Myocardial Infarction

Infarction of myocardial tissue due to complete vascular occlusion of a coronary artery (often from a ruptured coronary artery plaque). Presents with typical signs of angina. Complications include cardiogenic shock, pericarditis (3–5 days post-MI), arrhythmia (2 days post-MI), free wall rupture (4–10 days post-MI), LV failure, and death. Diabetes and hypertension are risk factors for sustaining a silent MI (an MI that does not cause pain).

- **Evolution of an MI.** Infarcted cardiac tissue undergoes coagulative necrosis, releasing inflammatory mediators and cardiac proteins into the bloodstream. As inflammatory cells move into tissue evidence of inflammation is seen. Vessel dilation and hyperemia occurs. Neutrophils migrate to necrotic tissue. Macrophages begin to accompany neutrophils and granulation tissue begins to form. Eventually inflammation decreases. Fibrosis and scar tissue replace normal cardiac tissue.

VALVULAR HEART DISEASE

Diseases of heart valves impose a hemodynamic burden on the heart by either restricting or obstructing the flow of blood. The most common valves affected are the aortic and mitral valves, with disease of the pulmonic and tricuspid valves not occurring as frequently. Abnormal valves are also more likely to become infected.

Rheumatic Fever

An acute immunologic reaction following a group A streptococcal infection affecting multiple systems (including the heart valves). Results from hypersensitivity reaction to M proteins. The cardiac manifestations include acute carditis and valvular abnormalities (thickened valves, abnormal motion of valves, and valvular vegetations).

Calcific Aortic Stenosis

Repetitive stress and motion of the aortic valve result in fibrosis and calcification leading to stenosis of the AoV, which results in increase in both preload and afterload on the heart. Approximately 2% of the population have a bicuspid AoV and are at a greater risk for developing calcific aortic stenosis. Associated with a harsh crescendo-decrescendo murmur occurring during systole.

Mitral Valve Prolapse

Accumulation of degenerated ground substance on the leaflets and chordae results in MV incompetence. During systole the increased pressure exerted on the MV from the LV results in its prolapse into the LA. Increased risk with Marfan's syndrome and other connective tissue disorders. Carries an increased risk of endocarditis, emboli, arrhythmias, and heart failure. The murmur is late systolic with a mid-systolic click.

Infective Endocarditis

Infection of the valve leaflets (or endocardium) causing a mass of thrombotic debris and infective material (vegetation) to develop on the valve. Signs and symptoms include Janeway's lesions, Roth's spots, Osler's nodes, nailbed hemorrhages, fever, and anemia. Complications include chordae rupture, glomerulonephritis, pericarditis, and systemic emboli. Risk factors include abnormal valves, IV drug use (typically affecting the tricuspid valve), dental or other surgical procedures, and infection.

- **Microbiology.** *S. aureus* is the most common organism associated with **acute** infective endocarditis. Subacute bacterial endocarditis is typically associated with less virulent organisms, most commonly α-hemolytic streptococci. Other bacteria include the Enterobacteriaceae and HACEK organisms (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella*).
- **Prosthetic cardiac valves.** Can be either biologic (bovine, porcine, or human) or synthetic. Any prosthetic valve carries a higher risk of infection and development of vegetations. Typical organisms are the coagulase-negative staphylococci (*S. epidermidis*).
- **Libman-Sacks endocarditis.** Sterile vegetations develop on the valve leaflets of patients with SLE.

MYOCARDIAL DISEASE

Myocarditis

Inflammation of the myocytes. Can be infectious, immune-mediated (post-viral, post-streptococcal, or due to SLE or drug reaction), or idiopathic (sarcoidosis or giant cell myocarditis).

Cardiomyopathy

Primary disease of the myocardium, excluding other causes of heart disease (hypertension, valvular disease, congenital disease, and myocarditis); commonly subdivided based on pathology:

- **Dilated cardiomyopathy.** Characterized by progressive cardiac dilation and hypertrophy resulting in diastolic dysfunction; Can be secondary to coxsackievirus infection, alcohol and cocaine abuse, nutritional disturbances (e.g., beri-beri), and toxic drug insults (e.g., doxorubicin). A special form is termed **peripartum cardiomyopathy** and occurs late in pregnancy.
- **Hypertrophic cardiomyopathy.** Also termed **asymmetric septal hypertrophy** or **idiopathic hypertrophic subaortic stenosis** (IHSS). Characterized by myocardial hypertrophy with abnormal diastolic filling and, in some instances, ventricular outflow obstruction. Known to cause sudden cardiac death in young athletes
- **Restrictive cardiomyopathy.** A disease of decreased ventricular compliance resulting in impaired ventricular filling. There are multiple etiologies, including endomyocardial fibrosis, eosinophilic endomyocar-

dial fibrosis (Loeffler's disease), and infiltrative diseases like amyloidosis, fibroelastosis, hemochromatosis, scleroderma, and radiation injury.

CONGENITAL HEART DISEASE: LEFT-TO-RIGHT SHUNTS

Results in blood flow from the left side of the heart to the right side. It is the most common type of congenital heart disease. Cyanosis is **not** an early presentation of this disease; cyanosis only appears **late**, after the disease produces sufficient pulmonary hypertension to result in reversal of the shunt, from right to left.

Atrial Septal Defects (ASDs)

The most common type is the **ostium secundum** ASD, which occurs when the septum secundum does not cover the ostium. Other ASDs are less common and include the **ostium primum** type, which occurs if the septum primum and endocardial cushions do not fuse. The least common is the **sinus venosus** ASD. A PFO exists in approximately 20% of the population and is typically asymptomatic. If audible, it results in a continuous diastolic murmur.

Ventricular Septal Defects (VSDs)

The most common congenital heart defect. However, most VSDs close spontaneously in childhood. The ventricular septum is formed by the fusion of the intraventricular muscular ridge and a thin membrane which grows downward from the endocardial cushion. The basal membranous region is the last portion to develop, and is the primary site for development of a VSD. If audible, it manifests as a continuous systolic murmur.

Patent Ductus Arteriosus (PDA)

Typically the ductus closes shortly after birth in response to increased arterial O_2, decreasing pulmonary vasculature resistance, and decreasing levels of prostaglandin E_2. Results in a machine-like murmur.

CONGENITAL HEART DISEASE: RIGHT-TO-LEFT SHUNTS

These shunts are typified by cyanosis shortly after birth, as unoxygenated blood flows from the right to left, bypassing the lungs.

Tetralogy of Fallot

The most common cyanotic congenital heart disease; consists of four components: (1) VSD, (2) overriding aortic root, (3) RV outflow obstruction, and (4) RV hypertrophy.

Transposition of the Great Arteries

The result of abnormal truncal separation, in which the aorta stems from the RV and the pulmonary artery from the left.

Coarctation of the Aorta

Narrowing of the aortic lumen, often associated with PDA, ASD, VSD, and Turner's syndrome. Important to distinguish whether the coaretation occurs pre–ductus arteriosus or post-ductally. The pre-ductal type presents in infancy. Can present as lower limb cyanosis, weak femoral pulses, and difference in BPs of the upper and lower limbs.

HEART MURMURS

See Table 1-45.

TABLE 1-45. Summary of Common Heart Murmurs

Etiology	Murmur and Characteristics
Mitral valve prolapse	Rumbling late systolic murmur with mid-systolic click heard best at the apex.
Mitral valve regurgitation	High-pitched blowing, holosystolic murmur heard at the apex with radiation to the left axilla.
Mitral stenosis	Rumbling, mid-diastolic murmur with opening snap heard at the apex.
Aortic regurgitation	High-pitched, blowing or Austin Flint (low-pitched rumble) diastolic murmur heard at the left sternal border. Associated with a wide pulse pressure.
Aortic stenosis	Mid-systolic, crescendo-decrescendo murmur heard at the second intercostal space with radiation to the carotids. Associated with pulsus parvus et tardus.
Atrial septal defect	Diastolic, rumbling murmur with a split S2 heard at the sternal border.
Ventricular septal defect	Blowing, holosystolic murmur heard at the sternal border.
Patent ductus arteriosus	Continuous, machinery-like murmur heard at the left sternal border. Loudest at time of S2.

PERICARDIAL DISEASE

Processes that affect the pericardial sac surrounding the heart. Pericardial disease is often a sign of another underlying condition. Presenting complaints involve chest pain that worsens with lying back and improves by leaning forward. Physical exam may show a coarse sound (friction rub). Fluid collections within the pericardial sac can be visualized with an echocardiogram or CT.

Pericarditis

Pericardial infection or inflammation. Typically infectious in origin (viruses are most common). Also seen with cardiac surgery, uremia, rheumatic fever, SLE, or mediastinal radiation.

- **Dressler's syndrome.** Pericarditis following an MI.
- **Cardiac tamponade.** May progress to tamponade (a fatal condition).

Pericardial Effusions

Fluid accumulation between the heart and pericardium. Accumulation of fluid may lead to decreased heart sounds. Fluid withdrawn by pericardiocente-

sis (placing a large needle transcutaneously into the pericardial sac to remove fluid) can be analyzed to determine the underlying cause.

- **Serous.** CHF, hypoalbuminemia; serosanguineous as a result of blunt chest trauma or malignancy.
- **Hemorrhagic.** Ruptured aortic root aneurysm, ruptured myocardium, or penetrating trauma.
- **Chylous.** Mediastinal lymphatic obstruction.

CARDIAC TUMORS

Tumors affecting the heart are rare. Presenting signs may be a new-onset heart murmur or signs of cardiac failure. They can be visualized with an echocardiogram.

Metastatic Neoplasms

Typically lung, breast, melanoma, and hematopoietic in origin.

Primary Neoplasms

Can be myxomas, lipomas, papillary elastofibromas, rhabdomyomas, angiosarcomas, and rhabdomyosarcomas.

- **Myxomas.** Benign tumors most commonly found in the LA. May cause serious complications if a fragment embolizes. Can cause valvular abnormalities.
- **Rhabdomyomas.** Most common cardiac malignancy of infancy and childhood. Associated with tuberous sclerosis.

NOTES

CHAPTER 2

Endocrine

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Hypothalamus and Pituitary

HORMONE BASICS

Homeostasis is maintained through the coordination of complex communication systems between cells, tissues, and organ systems. These interactions take place locally or at a distance and are mediated by peptides, amines, and steroids.

Site of Action

Signals can be characterized based on the relationship between the site of secretion and the relative location of receptors (see Figure 2-1):

- **Autocrine secretion:** Released signal affects the cell from which it was secreted (e.g., neoplastic growth advanced by growth factors (GFs) released by and acting on tumor → autocrine loop).
- **Paracrine secretion:** Released signal acts upon neighboring cells that have the appropriate receptors (e.g., upon exposure to an allergen, histamine is released and acts upon blood vessels to induce vasodilation → paracrine signaling).
- **Endocrine versus exocrine signals:** Endocrine signals are carried in the bloodstream. Exocrine signals are carried in ducts.

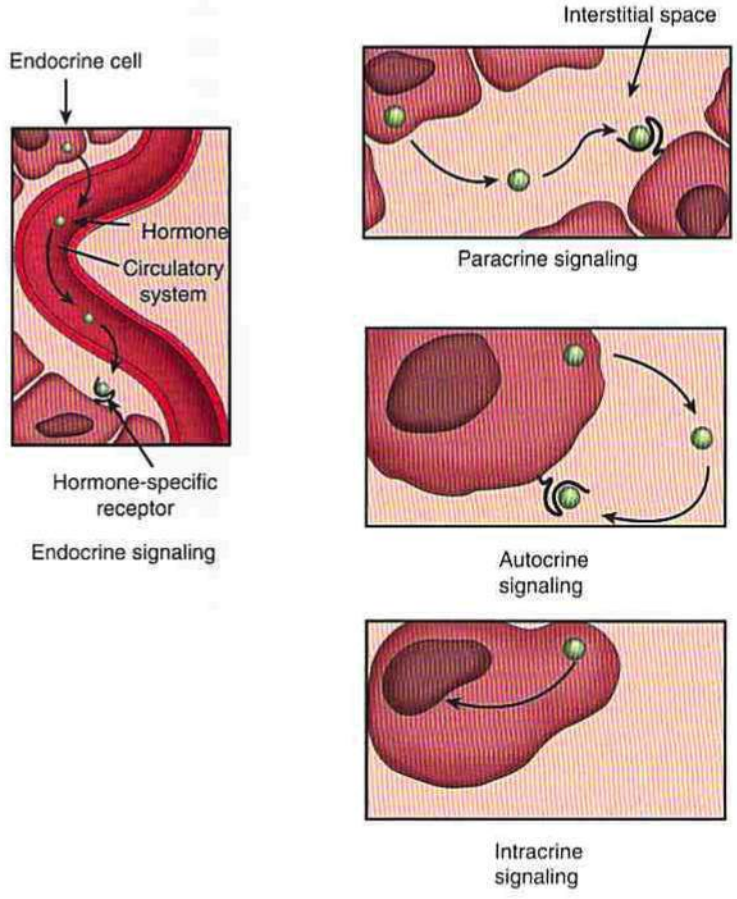


FIGURE 2-1. Modes of intercellular signaling: Autocrine, paracrine, and endocrine. (Modified, with permission, from Molina PE, *Endocrine Physiology*, 2nd ed, New York: McGraw-Hill, 2006: 5.)

- **Endocrine secretion:** Released signal enters the bloodstream and acts on distant receptors (e.g., follicle-stimulating hormone [FSH] is secreted from the anterior pituitary and acts on granulosa cells of the ovary → endocrine signaling).
- **Exocrine secretion:** Released signal enters duct and acts on epithelial surface of skin/gut (e.g., pancreas releases amylase into duodenum → exocrine secretion).
- **Multifunctional signals:** Signals can fall into multiple categories. They can produce different effects depending on the mode of action and the target tissue. For example, testosterone released by the testes acts on muscles to stimulate growth (endocrine), but also acts on seminiferous tubules to promote spermatogenesis (paracrine).

KEY FACT

The pancreas has both endocrine and exocrine functions. Its exocrine role includes facilitating the chemical digestion of food, while the endocrine pancreas regulates glucose metabolism.

KEY FACT

Endocrine signals enter blood. Exocrine signals are released into ducts.

Types of Hormones by Mechanism of Action

Hormones fall into three classes of molecules: Peptides, steroids, and amines. Each class differs in precursors, site of synthesis, plasma transport, and mode of action (see Table 2-1).

- **Peptides and proteins:** Preprohormone typically synthesized by rough endoplasmic reticulum (RER) → signal peptide cleavage in RER produces Prohormone → transport within Golgi apparatus results in further processing and final active hormone structure → **stored** in secretory vesicles → released via exocytosis → enter bloodstream (water soluble) → act on **cell surface receptors** of target tissues → act via **second messenger systems** (fast-acting effects)
- **Steroids:** Synthesized from cholesterol on demand **(not stored)** → lipid solubility allows for rapid diffusion across membrane → transported in blood bound to **carrier plasma proteins** because of limited solubility → diffuse across target cell membrane → bind **intracytoplasmic protein receptors** → resultant steroid hormone–receptor complex enters nucleus and activates transcription of specific genes → acts via new **protein synthesis** (slow-acting effects that require transcription/translation of new proteins)

TABLE 2-1. Peptide and Steroid Hormones

	Peptide/Protein Hormones	Steroid
Precursors	Amino acids	Cholesterol
Site of synthesis	Rough endoplasmic reticulum	Smooth ER
Storage	Yes (stored in vesicles)	No (produced on demand)
Carrier proteins	No (majority soluble in blood)	Yes, bound to carrier proteins
Location of receptors	Target cell membrane	Intracytoplasmic and transported into nucleus (steroid)
Signal propagation	Via second messengers	Via new gene transcription
Kinetics	Fast acting ± long-term actions	Slow acting
Examples	ACTH, LH, insulin	Estrogen, testosterone

- **Amines:** Synthesized from tyrosine precursors. Examples of amine hormones include thyroid hormone, epinephrine, and norepinephrine. Epinephrine and norepinephrine are synthesized, stored, released, and act on targets in a manner similar to peptide hormones. Thyroid hormone combines aspects of peptide and steroid hormones.

Plasma Transport of Lipid-Soluble Hormones

Peptide and protein hormones are soluble in circulation, but most steroid and thyroid hormones are hydrophobic. In order for these hormones to be soluble and to circulate in blood, they are bound to plasma proteins. These carrier proteins, produced by the liver, are both nonspecific and specialized for a given hormone.

- **Example:** Corticosteroid-binding globulin has a greater affinity for cortisol and aldosterone than other steroid hormones. Conversely, albumin is relatively nonspecific, binding a variety of steroid hormones with equal affinity (see Table 2-2).

Carrier proteins allow for another level of control within the signaling network, as hormone-protein complexes are unable to diffuse across membranes and activate target cells. Instead, an equilibrium exists between free and bound forms of hormone. Only free hormone is biologically active (i.e., it is able to diffuse across the plasma membrane and activate receptors). The amount of free hormone in plasma, therefore, determines how much hormone is available to target tissues.

Peptide Hormones: Second Messenger Pathways

Peptide/protein hormones stimulate membrane-bound receptors on target cells, generating conformational changes in the surface receptors. Activation of the hormone receptors results in intracellular propagation of the signal via the action of second messengers (see Table 2-3). The major second messenger systems include:

- **Adenylate cyclase mechanism:** Hormone binds G-protein coupled receptor (GPCR) → activated G protein (G_s) stimulates adenylate cyclase (AC) → AC catalyzes formation of cAMP → cAMP activates protein kinase A (PKA) → PKA exerts downstream effects via phosphorylation

TABLE 2-2. Hormone Transport Proteins

Carrier Protein	Hormone Transported	Serum Concentrations
Corticosteroid-binding globulin (CBG)	Cortisol, aldosterone	↓ in cirrhosis, nephrotic syndrome, and hypothyroidism.
Sex hormone-binding globulin (SHBG)	Estrogen, testosterone	↑ by estrogen, OCPs, and exogenous thyroid hormone.
Thyroxine-binding globulin (TBG)	Thyroxine, triiodothyronine	↑ by estrogen, pregnancy, and OCPs.
Serum albumin	Nonspecific steroid transporter, thyroxine, and triiodothyronine	↓ in cirrhosis, nephrotic syndrome, and protein malnutrition.

TABLE 2-3. Signal Propagation Mechanisms

Adenylate Cyclase	Inositol Triphosphate (IP_3)	Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT)	Intracellular Receptor
hCG	GHRH	Growth hormone	Glucocorticoids
TSH	Oxytocin	Erythropoietin	Estrogen
LH and FSH	GnRH	Leptin	Testosterone
ACTH	TRH	Cytokines	Progesterone
CRH			Vitamin D
Calcitonin			Triiodothyronine
PTH			
Glucagon			

- **Phospholipase C mechanism:** Hormone binds GPCR → activated G protein (G_q) stimulates phospholipase C → phospholipase C cleaves membrane lipids, producing inositol triphosphate (IP_3) and diacylglycerol (DAG) → IP_3 opens calcium channels in endoplasmic reticulum, releasing calcium into cytoplasm → calcium and DAG facilitate activation of protein kinase C (PKC) → PKC exerts downstream effects via phosphorylation
- **JAK/STAT mechanism:** Hormone binds cell surface receptor → activated Janus kinases (JAKs) phosphorylate tyrosine residues on surface receptor → signal transducers and activators of transcription (STATs) recruited and phosphorylated by JAKs → activated STATs dimerize and translocate to nucleus → modify gene expression

Regulatory Control

- **Receptor up- and downregulation:** Target cells can upregulate/downregulate the number of receptors or receptor affinity for their ligands.
- **Negative feedback:** A hormone or product of hormone signaling acts on an upstream endocrine organ to suppress further release of the original hormone. Feedback inhibition can occur via alterations in gene transcription, posttranslational processing, or hormone release (see Figure 2-2).
- **Positive feedback:** A hormone can effectively increase or decrease its own release via reinforcing properties along its endocrine axis.
  - Hormones may exhibit both positive and negative feedback controls (e.g., estrogen inhibits luteinizing hormone [LH] release during the follicular phase of the menstrual cycle [negative feedback], but at midcycle promotes the LH surge and ovulation [positive feedback]).

KEY FACT

Hypothalamic and posterior pituitary hormones such as gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), and oxytocin, respectively, use IP_3 (exception: corticotropin-releasing hormone [CRH]), whereas anterior pituitary hormones like TSH, adrenocorticotropic hormone (ACTH), and melanocyte-stimulating hormone (MSH) use cAMP. Antidiuretic hormone (ADH) uses both mechanisms.

HYPOTHALAMIC-PITUITARY AXIS

Hypothalamus

The hypothalamus is also known as the "master gland." It is located below the thalamus and above the pituitary gland, which is in the sella turcica. It contains several nuclei derived from **neuroectoderm**. Each nucleus contributes to maintaining **homeostasis:** water balance, body temperature, hunger, thirst, and emotions. The hypothalamus links the nervous system to the endocrine system, primarily through the pituitary gland. Ultimately, the hypothalamus regulates the timing and amount of pituitary hormones secreted.

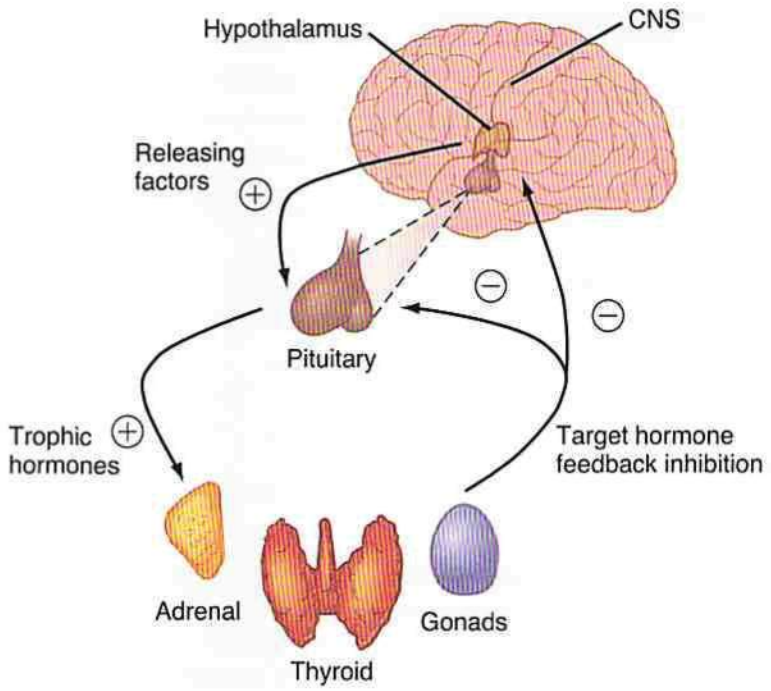


FIGURE 2-2. Feedback regulation. (Modified, with permission, from Kasper DL, Braunwald E, Fauci AS, et al, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 2072.)

FLASH FORWARD

In **empty sella syndrome**, the bony structures encompassing the pituitary are flattened, giving the impression of an enlarged and empty sella. Manifestations may include headache and, occasionally, endocrine dysfunction.

FLASH FORWARD

In **Sheehan's syndrome**, postpartum hemorrhage causing hypovolemic shock results in ischemic necrosis of the pituitary. This results in a loss of ACTH secretion, followed by losses of FSH, LH, and finally thyroid-stimulating hormone (TSH) secretion.

KEY FACT

Damage to the pituitary stalk leads to decreased secretion of all pituitary hormones except prolactin (PRL), whose secretion is increased.

FLASH FORWARD

Craniopharyngioma is a slow-growing tumor derived from remnants of Rathke's pouch.

The hypothalamus exerts direct control over anterior pituitary hormone secretion via releasing/inhibiting factors (see Table 2-4). These factors are synthesized by neural cell bodies in the hypothalamus, stored in granules at axon terminals, and released into the hypothalamo-hypophyseal circulation. Releasing/inhibiting factors include:

- CRH
- TRH
- Growth hormone–releasing hormone (GHRH)
- GnRH
- Somatostatin (inhibitory)
- Dopamine (inhibitory)

Pituitary

The pituitary, or hypophysis, is composed of two embryologically and morphologically distinct glands (anterior and posterior) connected to the hypothalamus by the hypophyseal stalk. The gland rests in a bony cavity at the base of the brain called the sella turcica (see Figure 2-3).

Anterior Pituitary

The anterior pituitary forms from the embryonic invagination of pharyngeal epithelium (oral ectoderm) called Rathke's pouch. It is composed of five different hormone-producing cell populations, all of which are regulated by hypothalamic releasing and inhibiting hormones. The neurons that secrete these releasing hormones converge in the median eminence of the hypothalamus, and act directly on the anterior pituitary via the hypophyseal circulation.

- The hypophyseal circulation constitutes a portal system, enabling high concentrations of hypothalamic releasing factors in the anterior pituitary, but near-undetectable levels elsewhere in the body.

TABLE 2-4. Overview of Hypothalamic Hormones

Hormone	Structure	Actions	Regulation
Corticotropin-releasing hormone	Peptide	Induces release of ACTH	Cortisol (–)
Gonadotropin-releasing hormone (GnRH)	Peptide	Induces release of LH and FSH	Testosterone (–), progesterone (–)
Growth hormone–releasing hormone	Peptide	Induces release of GH	GHRH (–)
Somatostatin (growth hormone–inhibitory hormone)	Peptide	Inhibits release of GH	Somatomedins (+), GH (+)
Prolactin-inhibiting factor (dopamine)	Amine	Inhibits release of prolactin	Prolactin (+)
Thyrotropin-releasing hormone	Peptide	Induces release of TSH and prolactin	

Posterior Pituitary (Neurohypophysis)

The posterior pituitary forms from neuroectoderm derived from the hypothalamus. During development, it fuses with Rathke's pouch. The posterior pituitary, composed of neural tissue, releases hormones in response to neuronal input (not releasing hormones).

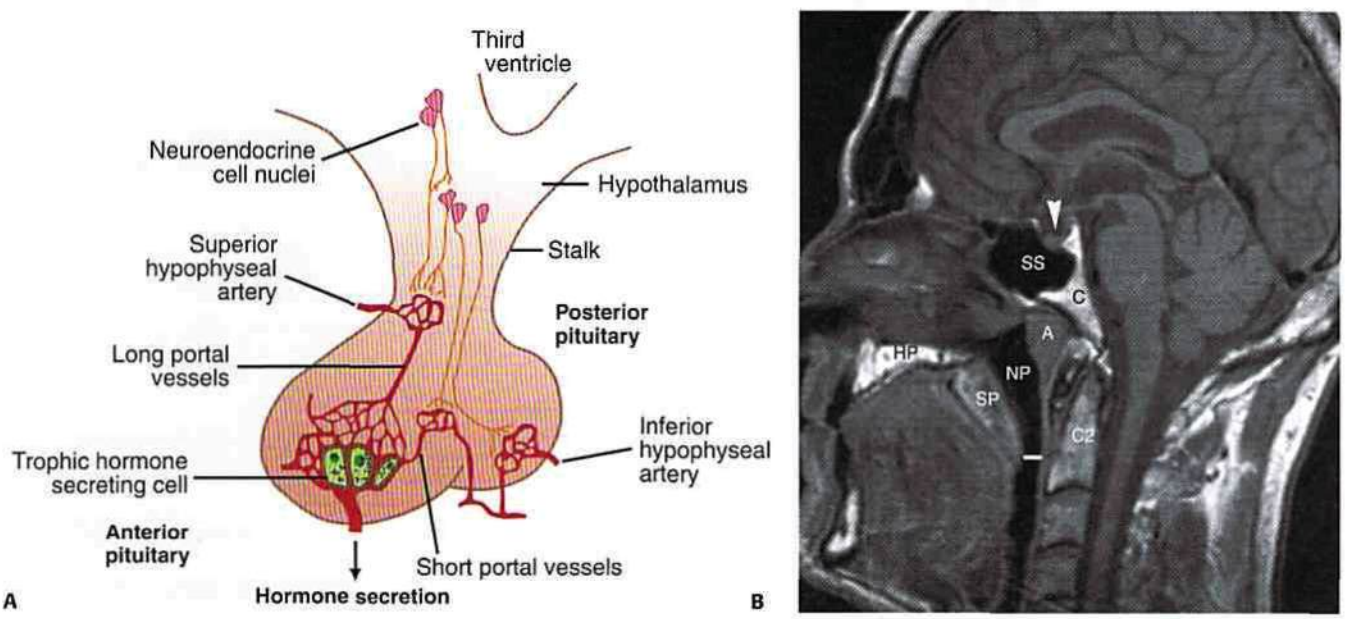


FIGURE 2-3. (A) Pituitary gland and (B) pituitary gland (white arrowhead) in sella turcica on T1-weighted MRI. (Part A modified, with permission, from Kasper DL, Braunwald E, Fauci AS, et al, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 2072. Part B reproduced, with permission, from Lalwani AK, *Current Diagnosis & Treatment in Otolaryngology—Head and Neck Surgery*, New York: McGraw-Hill, 2004: 45.)

KEY FACT

Anterior pituitary is derived from oral ectoderm. Posterior pituitary is derived from neuroectoderm.

MNEMONIC

Basophil-produced hormones:
FLAT BASe

FSH
LH
ACTH
TSH
BASophils

FLASH FORWARD

Prolactinomas are the most common pituitary tumors. Female patients present with galactorrhea and amenorrhea.

MNEMONIC

Somatostatin **stops** GH production, so it is "somatostatic."

Anterior Pituitary Cell Types and Regulation

The adenohypophysis is composed of five major cell types, each of which produces one or more peptide hormones (see Table 2-5).

Cell populations of the anterior pituitary can be further generalized according to reactions to histochemical stains. Periodic acid-Schiff (PAS) stain identifies three groups: Acidophils (stain orange), basophils (stain purple), and chromophobes (no stain reaction).

- **Acidophils:** Lactotropes (PRL), somatotropes (growth hormone)
- **Basophils:** Thyrotropes (TSH), corticotropes (ACTH), gonadotropes (FSH, LH)
- **Chromophobes:** "Empty" cells (lack cytoplasmic granules); may be former acidophils or basophils after release of hormone-containing granules

Anterior Pituitary Hormones

Prolactin

PRL is structurally homologous to growth hormone (GH) and human placental lactogen (HPL). It is synthesized in the RER by lactotropes.

- Suckling stimulates PRL secretion.
- Dopamine tonically inhibits PRL secretion.
- PRL promotes additional breast development during pregnancy (in concert with several other hormones) in preparation for milk production, stimulates lactation (primary role), and inhibits ovulation through its effects on GnRH.
- Thus, PRL levels are low in the nonpregnant woman or pregnant woman prior to suckling (see Figure 2-4).

Growth Hormone

GH is a polypeptide hormone whose main function is to promote linear growth.

- GH is also referred to as somatotropic hormone or somatotropin.
- GH release is under hypothalamic regulation: GHRH promotes and somatostatin inhibits GH release.
- GH acts directly on tissues; its growth-promoting effect is primarily mediated via insulin-like growth factor-1 (IGF-1) formerly known as somatomedin.
  - IGF-1 is produced by the liver in response to GH.
  - GH and IGF-1 produce metabolic changes that stimulate growth of tissues (see Table 2-6 for direct and indirect effects of GH).

TABLE 2-5. Anterior Pituitary Hormones

Cell Type	PAS Stain Pattern	Hormone	Target Organ
Lactotropes	Acidophil	Prolactin	Ovaries, mammary glands
Somatotropes	Acidophil	Growth hormone	Liver, adipose tissue
Thyrotropes	Basophil	TSH	Thyroid
Corticotropes	Basophil	ACTH	Adrenal gland
Gonadotropes	Basophil	FSH, LH	Ovaries, testes

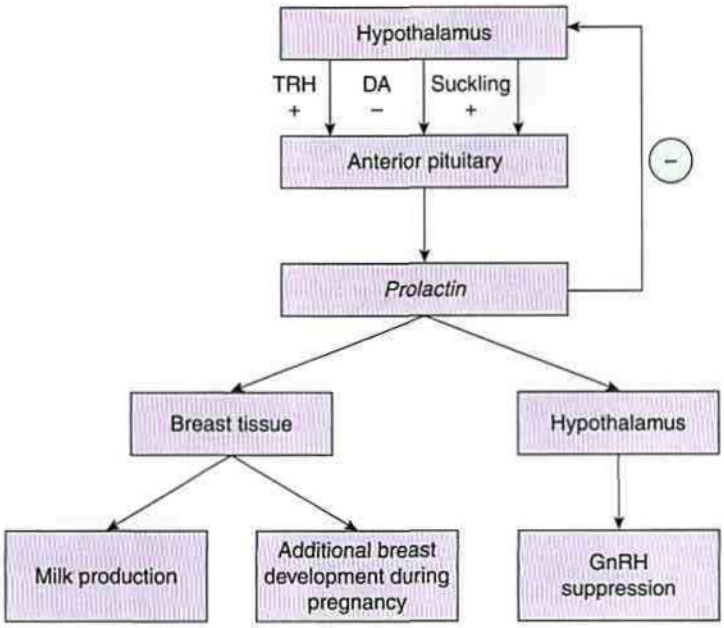


FIGURE 2-4. Regulation of prolactin. DA = dopamine.

- The metabolic effects of GH include increased protein synthesis and fat utilization, and decreased glucose uptake into tissues.
- GH is not as selective for target tissues as other pituitary hormones; it exerts its effects throughout most of the body.
- GH is secreted in a pulsatile pattern; at any moment in time, serum GH concentrations are usually low. After adolescence, GH production decreases, but continues at a lower rate during adult life.
- GH is under hypothalamic control, but also responds to exercise, trauma, and acute hypoglycemia (see Figure 2-5 for regulation).
- GH, like glucagon, cortisol, and epinephrine, is a counterregulatory hormone that is released in response to hypoglycemia. Counterregulatory hormones increase serum glucose levels by promoting glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis.

TABLE 2-6. Effects of Growth Hormone (GH) and Insulin-like Growth Factor-1 (IGF-1)

Direct Effects of GH	Indirect Effects of GH (Through IGF-1)
Decreases glucose uptake (counterregulatory effects).	Stimulates protein synthesis at the organ level.
Stimulates protein synthesis in muscle.	Stimulates protein synthesis in muscle.
Mobilizes fatty acids.	Increases protein synthesis in chondrocytes (promotes linear growth).
Increases lean body mass.	Increases lean body mass.
Promotes IGF-1 secretion.	

FLASH FORWARD

Excessive GH secretion from a pituitary adenoma results in **acromegaly** that causes overgrowth of the face, extremities, and visceral organs, and may cause hyperglycemia (glucose intolerance or frank diabetes mellitus [DM]).

FLASH FORWARD

Gigantism occurs if a pituitary adenoma develops prior to growth plate fusion. Patients are excessively tall.

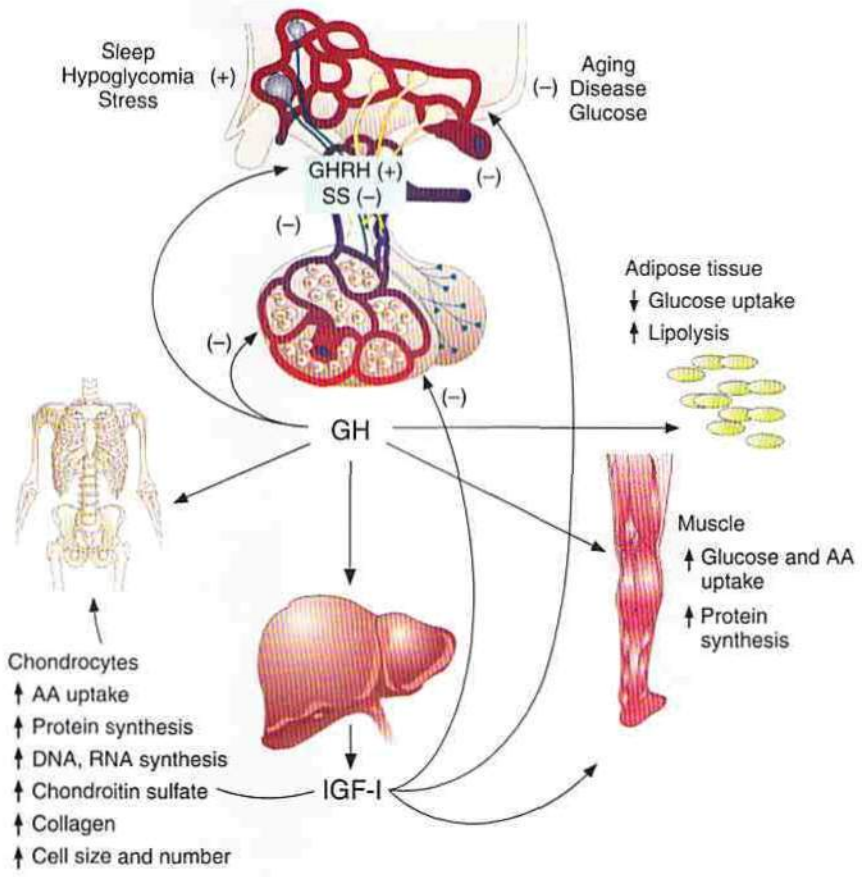


FIGURE 2-5. GH regulation. Factors that inhibit GH secretion are IGF-1 and somatostatin (SS). Factors that promote GH secretion are GHRH, hypoglycemia, exercise, stress, sleep, and amino acids (arginine and leucine). (Modified, with permission, from Molina PE, *Lange Endocrine Physiology*, 2nd ed, York, PA: McGraw-Hill, 2006: 56.)

FLASH FORWARD

Excess ACTH may be produced by pituitary adenomas or ectopic sites, such as small cell carcinomas of the lung. Individuals with supraphysiologic levels of ACTH exhibit the features of **Cushing's syndrome**.

FLASH FORWARD

Addison's disease, or primary adrenal insufficiency, results in elevated ACTH levels. Patients have hyponatremia, volume depletion, hyperkalemia, hypotension, weakness, and skin hyperpigmentation (increased MSH).

FLASH FORWARD

Secondary and tertiary adrenal insufficiency caused by pituitary or hypothalamic damage, respectively, cause cortisol deficiency but do not cause hyperpigmentation (decreased ACTH, and thus decreased MSH). Because aldosterone secretion is primarily regulated by the renin-angiotensin system (RAS), these patients do not typically have hyponatremia and hyperkalemia.

Adrenocorticotropic Hormone

ACTH is a polypeptide hormone that stimulates corticosteroid production by the adrenal cortex.

- ACTH is synthesized by corticotropes in the anterior pituitary gland in response to stimulation by CRH.
- ACTH is synthesized from a larger precursor, proopiomelanocortin (POMC); β-lipotropin and β-endorphin are also derived from POMC (see Figure 2-6).
- A bioactive moiety, α-MSH, is present on the N-terminal end of ACTH.
- ACTH regulates the size, integrity, and synthetic function of the adrenal cortex.

Anterior Pituitary Hormone Homology

The anterior pituitary gland produces six major hormones that can be classified into three groups based on structural homology.

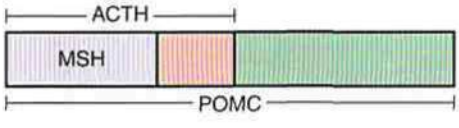


FIGURE 2-6. Composition of proopiomelanocortin (POMC). MSH = α-melanocyte-stimulating hormone.

TABLE 2-7. Summary of Anterior Pituitary Hormone Function and Regulation

Hormone	Structure	Actions	Regulation
Adrenocorticotropic hormone (ACTH)	Peptide	Induces synthesis of adrenal cortical hormones (cortisol, androgens, aldosterone).	Cortisol (–)
Follicle-stimulating hormone (FSH)	Peptide	Stimulates follicle growth in ovaries and sperm maturation in testes.	Inhibin (–), estrogen (–), progesterone (–)
Luteinizing hormone (LH)	Peptide	Promotes testosterone synthesis in testes; surge causes ovulation; promotes estrogen/progesterone synthesis in ovaries.	Testosterone (–), estrogen (+/-), progesterone (–)
Growth hormone (GH)	Peptide	Promotes protein synthesis and tissue growth.	Somatomedins (–)
Thyroid-stimulating hormone (TSH)	Peptide	Stimulates growth of thyroid gland and synthesis and secretion of thyroid hormones.	Thyroid hormones (–)
Prolactin	Peptide	Causes milk production in breast.	Dopamine (–), TRH (+)

- **Glycoproteins:** FSH, LH, and TSH are each comprised of α and β subunits. They share an identical α subunit, but each has a unique β subunit (see Table 2-7).
- **Somatomammotropins:** GH and PRL are structurally related peptide hormones that belong to the same cytokine-hematopoietin family.
- **ACTH-related peptides:** ACTH, MSH, and lipotropin are formed by cleavage of a single large precursor molecule (POMC).

Posterior Pituitary

Hormones of the posterior pituitary are synthesized by hypothalamic neurons and transported via axoplasmic flow to axon terminals in the posterior lobe of the pituitary. These hormones include oxytocin and ADH, also referred to as vasopressin. The hypothalamic nuclei responsible for hormone production are the paraventricular nuclei and supraoptic nuclei.

- Hormone-producing neurons are referred to as magnocellular neurons because of their large cell bodies (see Figure 2-7).

Oxytocin and ADH are synthesized from larger precursors (prohormones), which are enzymatically cleaved within vesicles to produce active hormone. Release of oxytocin or ADH-containing granules is regulated by exogenous and endogenous stimuli, which are transformed into CNS signals.

KEY FACT

Hormones of the anterior pituitary are regulated by releasing/inhibiting factors secreted into the hypophyseal circulation. Posterior pituitary hormones are controlled by neurotransmission.

Oxytocin

Two main actions (see Figure 2-8):

- Promotes uterine contractions during labor
- Stimulates contraction of myoepithelial cells in the breast, facilitating milk delivery to suckling infant

Exogenous stimuli drive oxytocin secretion; signals include suckling of infant on breast and dilation of cervix (as in childbirth).

FLASH FORWARD

Oxytocin promotes contraction of the myometrium and is often used in obstetrics to induce or augment labor.

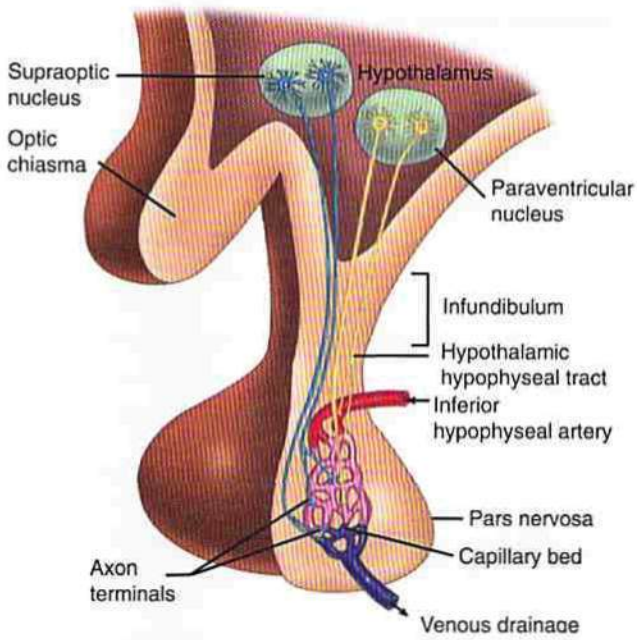


FIGURE 2-7. Hypophyseal circulation and associated nuclei.

ANTIDIURETIC HORMONE

ADH plays a central role in osmoregulation.

- The osmotic concentration of extracellular fluid (ECF) is sensed by specialized neurons within or adjacent to the hypothalamus. The size of these

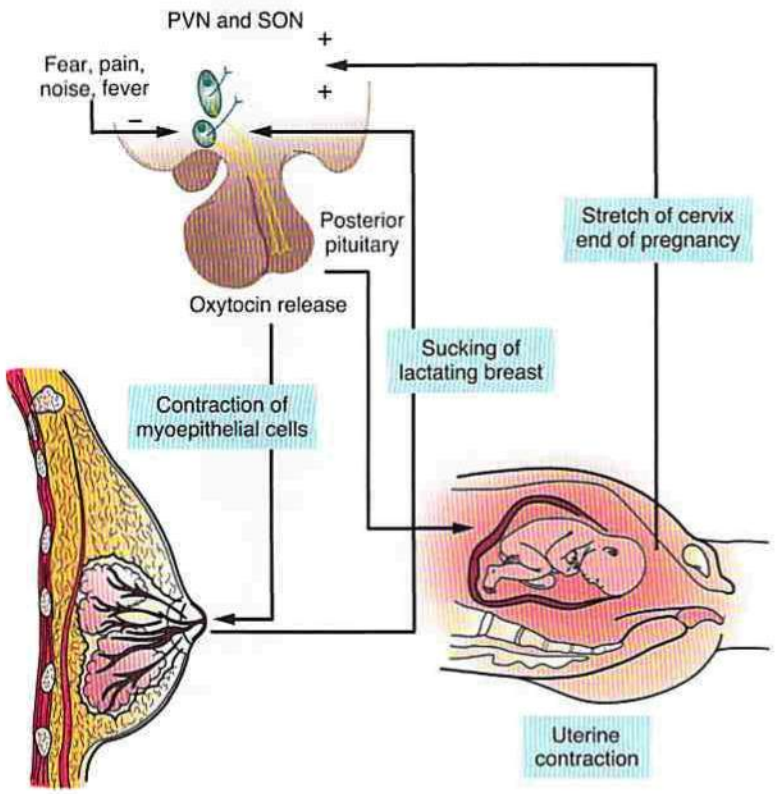


FIGURE 2-8. Oxytocin effects and regulation. PVN = paraventricular nuclei; SON = supraoptic nuclei. (Modified, with permission, from Molina PE, *Lange Endocrine Physiology*, 2nd ed, New York: McGraw-Hill, 2006: 35.)

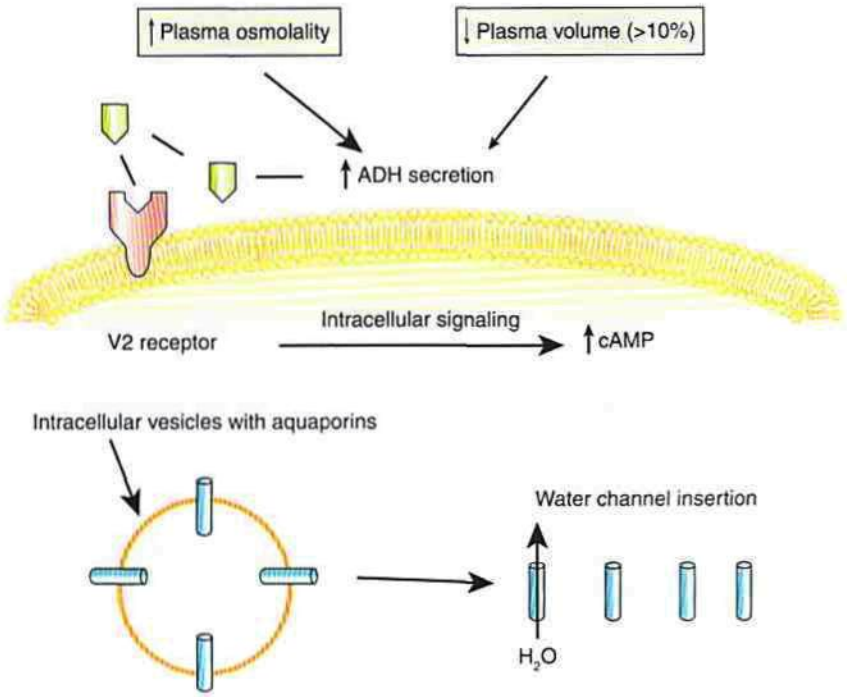


FIGURE 2-9. ADH signaling and aquaporin insertion.

neurons changes with extracellular osmolality, resulting in nerve signals increasing/decreasing ADH secretion.

- ADH secretion increases in hyperosmolar conditions.
- ADH increases permeability to water in the distal tubules and collecting ducts of the kidney, thereby increasing water reabsorption and decreasing plasma osmolality.
- ADH triggers water channel insertion, which allows water (and urea) to be passively absorbed:
  - It stimulates membrane-bound V2 receptors, which triggers an increase in intracellular cAMP. Special vesicles containing aquaporins (permeable water pores) are inserted into the luminal aspect of the cell membrane. Free diffusion of water occurs from tubule to peritubular fluid, decreasing ECF osmolality (see Figure 2-9).
- In addition to the stimulus of increased ECF osmolality, ADH is secreted in response to large decreases (> 10%) in blood volume (see Table 2-8).

TABLE 2-8. Factors Affecting Secretion of ADH

Increase ADH Secretion	Decrease ADH Secretion
↑ Plasma osmolality	↓ Plasma osmolality
↓ Plasma volume[a]	↑ Plasma volume[a]
↓ BP	↑ BP

[a]ADH secretion is affected by large changes in plasma volume.

FLASH FORWARD

The syndrome of inappropriate (SIADH) has many causes. Tumors, including small cell carcinoma of the lung, can result in paraneoplastic syndromes. Tumor production of ADH results in abnormally high levels of ADH and hyponatremia.

FLASH FORWARD

Diabetes insipidus (DI) is characterized by a deficiency of ADH, which may be due to a host of factors including tumors, trauma, pituitary surgery, and inflammation. DI can be central (due to decreased ADH production) or nephrogenic (due to decreased renal responsiveness to ADH). The latter may be caused by medications (e.g., lithium).

FLASH FORWARD

Decreased ADH production can also be due to **primary polydipsia.** Increased water intake results in a physiologic reduction in ADH secretion.

- At high concentrations, ADH constricts arterioles through the V1 receptor. Consequently, ADH is also referred to as arginine vasopressin.
- When blood loss occurs, ADH secretion is stimulated by signals from atrial stretch receptors and baroreceptors.
  - Hypovolemia with resultant reduced atrial stretch results in decreased secretion of atrial natriuretic peptide (ANP). Low levels of ANP support increased secretion of ADH.
  - Baroreceptors of the aortic arch and carotid sinus sense decreased arterial pressure due to hypovolemia, resulting in decreased afferent signals to the medulla and consequent increase in ADH secretion and sympathetic stimulation.
    - Unlike the RAS, which responds to subtle variations in circulating volumes, ADH secretion responds only to large decreases in blood volume.

Pituitary Tumors

Pituitary tumors may consist of hypersecreting, hyperproliferative adenomas or hyposecreting adenomas (30%–40%). Syndromes are due to the effect of excess hormone if present, suppression of other hormones due to compression, and/or elevated intracranial pressure due to mass effect.

ANTERIOR PITUITARY DISEASE

Prolactinoma

The average age of onset is 20–40 years. This tumor accounts for 50% of pituitary adenomas, and is characterized by hypersecretion of PRL. The characteristic elevated PRL induces lactation, which in turn inhibits GnRH. Decreased GnRH leads to decreased FSH and LH, which are in turn responsible for the signs seen on presentation. Other causes of elevated PRL include nipple stimulation (as estrogen and progesterone block PRL's action on its target tissues, breast and ovaries).

Dopamine tonically **inhibits** the anterior pituitary, so its depletion or pharmacologic antagonism disinhibits the anterior pituitary and PRL production. Excess PRL arises in the context of pathologic inhibition of dopamine production (hypothyroidism), and drugs that inhibit the synthesis of dopamine or drugs that deplete dopamine (reserpine, methyldopa). In hypothyroidism, elevated TRH stimulates the anterior pituitary to upregulate PRL production.

Presentation

Amenorrhea, infertility, galactorrhea; decreased libido and osteopenia due to decreased estrogen in women; impotence and gynecomastia in men.

Diagnosis

- Serum chemistry: Elevated PRL. Rule out false-positives by screening for hypothyrodism, pregnancy, antiemetic/antipsychotic medications, renal failure, stress, high-carbohydrate diet, and cirrhosis as causes.
- CT scan or MRI to identify mass lesions.

Treatment

- Asymptomatic patients without headache or hypogonadism can be followed with serial MRIs.
- Symptomatic patients can be offered medical therapy with dopamine agonists such as bromocriptine, or surgical resection and radiotherapy if

tumor causes significant compression or disease is unresponsive to medical therapy.

Gigantism and Acromegaly

This disorder of excessive GH secretion manifests differently in children, in whom the epiphyses have not yet closed, versus adults. It leads to gigantism in children and acromegaly in adults. **Gigantism** refers to excess linear height of more than 2 SD above the mean for a person's age, sex, and Tanner stage; this results from excess GH acting on the epiphyseal growth plates. Acromegaly is the same disorder, resulting from GH acting on the fused growth plate cartilages in adults. GH excess is most commonly caused by a pituitary adenoma composed of somatotroph cells. Less common causes include hypothalamic GHRH secretion or disruption of somatostatin tone.

Gigantism is rare, with approximately 100 reported cases to date. The incidence of acromegaly is 3–4 cases per million, and the prevalence is 40–70 cases per million. Mean age of onset for acromegaly is in the third decade. The onset of acromegaly is insidious, as opposed to the dramatic presentation of gigantism.

Presentation

- Musculoskeletal and visceral overgrowth and deformity (gigantism) in children
- Acromegaly (enlarged jaw, hands, feet, coarsening facial features, prognathism)
- Enlarged liver and heart (cardiomyopathy)
- Peripheral neuropathies such as carpal tunnel syndrome secondary to nerve compression
- Glucose intolerance and frank DM in one-sixth of cases; also amenorrhea and impotence
- Headache due to mass effect, and bitemporal hemianopsia due to superior growth of tumor leading to compression of the optic chiasm

Diagnosis

- Elevated serum IGF-1 (sensitive screening test)
- Failure of glucose to suppress GH on oral glucose tolerance test (OGTT)
  - OGTT: Administer 100 grams of glucose to suppress GH, and then measure GH levels. Failure to suppress GH to < 5 ng/dL within 3 hours is diagnostic.
- CT or MRI scans to localize the tumor

Treatment

- Bromocriptine, a dopamine agonist, works in one-quarter of cases
- Octreotide is a long-acting somatostatin analog that can lower GH levels to normal, and works in approximately two-thirds of patients
- Pegvisomant (GH-receptor antagonist)
- Transsphenoidal surgery and radiotherapy

Prognosis

Cardiac failure is the most common cause of death in acromegalic patients. They also suffer an increased risk of colon cancer and pituitary insufficiency.

Panhypopituitarism

This refers to a reduction in the release of all pituitary hormones, and may result from both primary and secondary causes. Primary events that disrupt

TABLE 2-9. Clinical Findings with Hypopituitarism

Hormone	Normal Function	Clinical Findings in Hormone Deficiency
GH	Growth and glucose homeostasis	Children: growth failure, dwarfism. Adults: fatigue, osteoporosis, often not detectable (skin wrinkles and increased sensitivity to insulin, manifesting as hypoglycemia).
Gonadotropin (LH/FSH)	Menstrual cycle and reproduction	Amenorrhea, genital atrophy, infertility, ↓ libido, ↓ axillary/pubic hair, impotence.
TSH	Stimulates thyroxine production from the thyroid gland	Resembles central hypothyroidism without goiter (cold intolerance, lethargy); normal or TSH inappropriately low in the setting of low thyroxine.
ACTH	Stimulates glucocorticoid production from the adrenal gland	Resembles primary adrenal insufficiency, with fatigue, orthostatic hypotension, **but without** skin hyperpigmentation, hypokalemia, salt craving, ↓ response to stress.

KEY FACT

Ischemic necrosis of the pituitary **(Sheehan's syndrome).** Because the anterior pituitary increases to almost twice its size during pregnancy, if there is reduced O_2 supply due to postdelivery hemorrhage or shock, the sudden hypotension can lead to anterior pituitary dysfunction.

the hypothalamus or pituitary include surgery, radiation, tumors, apoplexy (sudden hemorrhage into the gland, usually from adenoma), infection, infiltration by sarcoid or hemochromatosis, ischemia (Sheehan's syndrome), carotid aneurysm, and cavernous sinus thrombosis and trauma. Secondary causes refer to disease that disrupts the hypothalamus or pituitary stalk, including tumors, surgery, infection, infiltration, and trauma.

Presentation

The sequence of hormonal loss is GH → FSH/LH → TSH → ACTH, with the resultant symptoms based on the temporal order of hormonal deficit (see Table 2-9).

Diagnosis

Low levels of the specific pituitary hormones and low target gland hormones. MRI of the brain may localize the tumor for preoperative planning.

Treatment

Replacement of the missing hormones, with the most important being cortisol for protection against infection. Because most of the anterior pituitary hormones are proteins or glycoproteins that induce the secretion of other hormones, the target gland hormone is often used as replacement rather than the pituitary hormone (i.e., TSH replaced with thyroxine, ACTH replaced with hydrocortisone or another glucocorticoid, LH and FSH replaced with testosterone, estrogen, or progestin).

POSTERIOR PITUITARY DISEASE

Diabetes Insipidus

Characterized by a deficiency of ADH and results in inappropriately dilute urine. Vasopressin (ADH), synthesized by the supraoptic nucleus and stored in the axon terminals of the posterior pituitary, functions to concentrate urine and conserve water. There are two types of DI.

TABLE 2-10. Causes of Diabetes Insipidus (DI)

Central DI	▪ Idiopathic (50% of cases) ▪ Trauma, surgery ▪ Tumors, sarcoidosis, TB ▪ Hand-Schüller-Christian disease
Nephrogenic DI	▪ Hypercalcemia, hypokalemia ▪ Medications: Lithium, demeclocycline ▪ Pyelonephritis

- Central DI, due to insufficient release of ADH from the posterior pituitary.
- Nephrogenic DI, with normal ADH secretion but target tissues (kidneys) that are unresponsive (renal resistance to the ADH). Causes are listed in Table 2-10.

Presentation

Excessive urination and thirst. In children, DI can present with fever, vomiting, and diarrhea.

- The high serum osmolality stimulates thirst, causing patients to drink large amounts of water.
- Hypernatremia is usually not significant if the patient has access to water, but may be a problem in hospitalized or debilitated patients with water restriction or unrecognized DI.

Diagnosis

- **Vasopressin challenge:** Injection of vasopressin → increased U_{Osm} in central DI, but not nephrogenic DI (see Table 2-11).
- UA: Low U_{Osm} and high P_{Osm} in both central and nephrogenic DI, as the kidneys either do not receive ADH or cannot respond to ADH in both cases.
  - Meanwhile, U_{Osm} and P_{Osm} are both low in primary polydipsia, since kidneys do work appropriately and put out dilute urine.

Treatment

- Vasopressin (subcutaneously, orally, or intranasally) for central DI.
- Chlorpropamide increases the release of ADH in partial ADH deficiency.
- For nephrogenic DI, diuretics such as hydrochlorothiazide (HCTZ). HCTZ is sometimes used with amiloride to prevent hypokalemia.

TABLE 2-11. Differentiating between Central and Nephrogenic Diabetes Insipidus (DI)

	Increase in U_{Osm} with Water Deprivation?	Response to Injection of ADH?
Central DI	No	Yes
Nephrogenic DI	No	No
Primary polydipsia	Yes	Yes

Prognosis

Patients who have access to water can usually make up for the large urinary losses. When water is not readily available, the rising serum sodium concentration can cause weakness, fever, prostration, and potentially death.

Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)

Excess ADH in the absence of hyperosmolarity leads to an inability to dilute urine. There is a net gain in free water over sodium, resulting in euvolemic hyponatremia. Common causes of SIADH include CNS disease; pulmonary diseases such as tumor; endocrinopathies; and drugs including NSAIDs, antidepressants, chemotherapeutics, diuretics, phenothiazines, and hypoglycemics. This is summarized in Table 2-12.

Presentation

Often without symptoms if SIADH is chronic. If acute onset, can cause brain swelling, leading to lethargy, weakness, seizures, and coma/death.

- SIADH causes volume expansion, but edema and hypertension are usually not present because of natriuresis (excreting excess sodium in urine).

Diagnosis

Hypotonic hyponatremia decreases serum Na, and P_{Osm} in the presence of increased $U_{Osm} > 300$ mOsm/L (normal = 290 mOsm/L).

- Need to rule out hypothyroidism (reduced CO, GFR) and adrenal insufficiency (increased CRH and ADH).
- Also decreased BUN and Cr, reflecting diluted fluid stores.

KEY FACT

Hyponatremia should not be corrected too quickly because this can result in central pontine myelinolysis.

Treatment

Fluid restriction in mild cases of SIADH. When fluid restriction is not feasible or not working, use demeclocycline or conivaptan, which inhibits the action of ADH on the kidneys. Hypertonic saline may be used if cerebral edema, convulsions, or coma develops. Hyponatremia should not be corrected too quickly because this can result in central pontine myelinolysis.

TABLE 2-12. Common Causes of SIADH

Neoplasms with ectopic ADH secretion	▪ Small cell lung carcinoma ▪ Thymoma
Pulmonary diseases	▪ TB ▪ Lung abscesses ▪ Pneumonia
CNS disorders	▪ Skull fractures/trauma ▪ Subdural hematoma
Drugs	▪ Chlorpropamide ▪ Vincristine, vinblastine ▪ Cyclophosphamide ▪ Carbamazepine

PITUITARY/HYPOTHALAMIC PHARMACOLOGY

Leuprolide

Mechanism

GnRH is normally secreted in a pulsatile fashion by the hypothalamus, and stimulates the release of FSH and LH from the anterior pituitary. Leuprolide is a GnRH analog that has a longer half-life, and can be used in a pulsatile fashion to increase LH/FSH, or continuously to suppress LH/FSH.

Uses

When given in a pulsatile fashion, it is used to treat women with amenorrhea. When given in a continuous fashion, leuprolide suppresses the growth of prostate cancer and endometriosis.

Side Effects

Bone pain, feet/ankle swelling, reduced sexual desire.

Somatotropin

Mechanism

GH analog, increases muscle mass.

Uses

Dwarfism; treats wasting associated with AIDS or malignancy.

Side Effects

Hand/foot edema, thickening of bones/jaw, carpal tunnel syndrome, increased organ growth, decreased insulin sensitivity, hyperglycemia.

Octreotide

Mechanism

Somatostatin is a hypothalamic hormone that normally inhibits the release of GH, glucagon, insulin, gastrin, and vasoactive intestinal peptide (VIP). Octreotide is a somatostatin analog that has a longer half-life than somatostatin itself.

Uses

Variceal bleeding, VIPomas, carcinoid syndrome.

Side Effects

Gallbladder problems, pancreatitis, hypo- or hyperthyroidism.

Dopamine Agonists (Bromocriptine, Cabergoline)

Mechanism

Dopamine receptor agonists. PRL secretion is normally inhibited by dopamine from the hypothalamus.

Uses

Prolactinomas, Parkinson's disease.

Side Effects

Dizziness, lightheadedness, confusion.

Desmopressin

Mechanism

Analog of vasopressin (ADH). Has minimal V1 activity (minimal action on vascular smooth muscle). More effect on V2 receptors, which act on the renal collecting tubules to increase water reabsoprtion. Also stimulates release of von Willebrand's factor (vWF) from the endothelium in platelet dysfunction disorders.

Uses

Central DI; von Willebrand's disease.

Side Effects

Transient headache, flushing.

Oxytocin

Mechanism

Posterior pituitary hormone that stimulates milk secretion and induces uterine contractions during labor.

Uses

Induces labor; decreases postpartum bleeding by inducing contractions.

Side Effects

Chest pain, confusion, excessive vaginal bleeding, palpitations, seizures.

Thyroid and Parathyroid

THYROID

The thyroid gland regulates growth and metabolic rate through the actions of its two major hormones, thyroxine (T_4) and triiodothyronine (T_3). A relative deficiency or excess of thyroid hormone may become manifest clinically through alterations in energy, weight, temperature tolerance, GI function, and hair/skin quality. The parafollicular (C) cells of the thyroid gland produce **calcitonin**, a hormone that lowers serum calcium levels; however, it does not play a significant role in calcium metabolism in humans.

Anatomy

Situated anterior to the trachea, the thyroid is a butterfly-shaped structure below the larynx extending from C5 to T1. It is composed of a right and left lobe united by a thin strip of thyroid tissue called the isthmus (see Figure 2-10).

The thyroid is among the largest endocrine organs, weighing 10–20 grams. It receives a disproportionately large share of cardiac output per gram of tissue. The rich blood supply of the thyroid is derived from two pairs of vessels: the superior and inferior thyroid arteries.

- Superior thyroid artery: First branch off the external carotid artery and supplies the superior half of the thyroid.
- Inferior thyroid artery: Stems from the thyrocervical trunk, which is a branch of the subclavian artery.

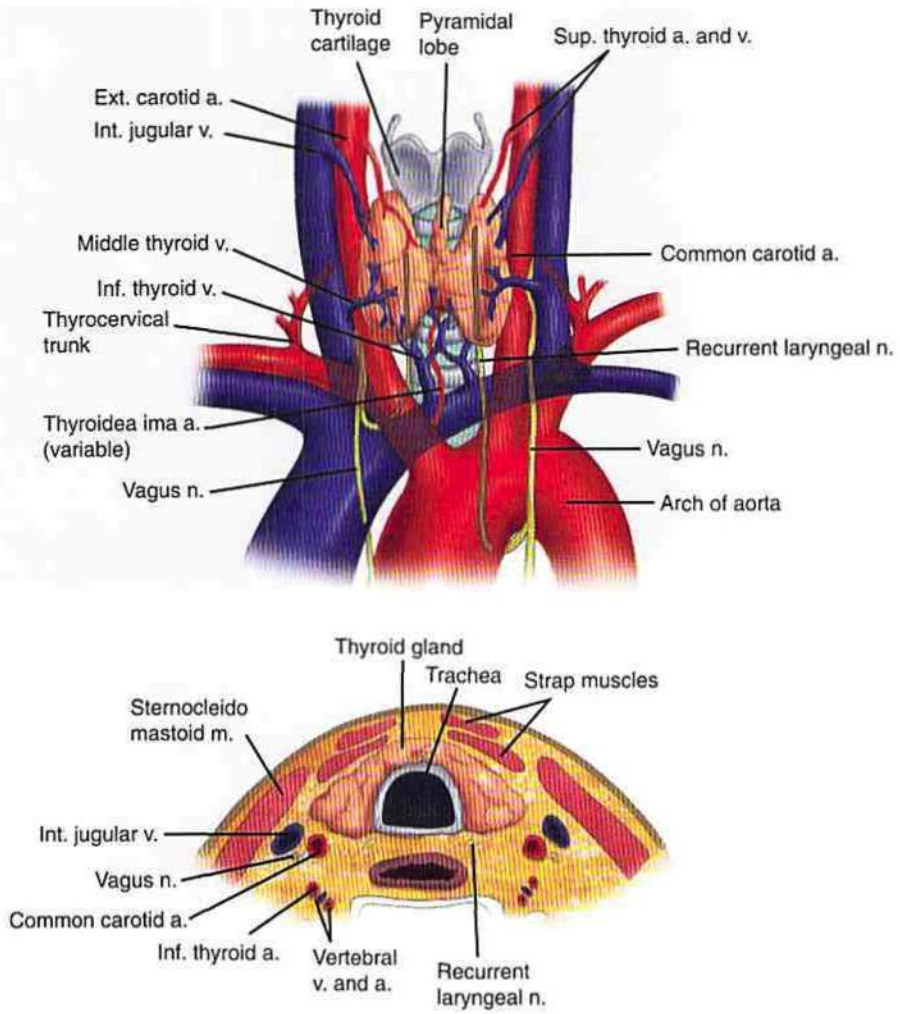


FIGURE 2-10. Anatomy of the thyroid gland.

- *Three sets of veins drain the thyroid: Superior, middle, and inferior thyroid* veins. The superior and middle veins drain into the internal jugular veins, whereas the inferior thyroid veins empty into the brachiocephalic veins.

Embryology

The thyroid is formed from an epithelial outpouching, the **thyroid diverticulum**, which develops in the floor of the foregut at 3–4 weeks of gestation. The thyroglossal duct progenitor migrates caudally and the thyroid gland eventually assumes its normal position below the larynx unless migration is disrupted. This duct remains patent during development, maintaining a connection between foregut and thyroid. Ultimately, the thyroglossal duct closes, leaving the foramen cecum as an adult remnant. The thyroid begins secreting hormone as early as the 18th week of fetal development.

Histology

At the microscopic level, the thyroid gland is made up of spherical, closed follicles that are lined with cuboidal epithelial cells.

- The basal surfaces of follicular cells are in contact with a rich blood supply that allows for the absorption of iodide to be used in hormone production.

FLASH FORWARD

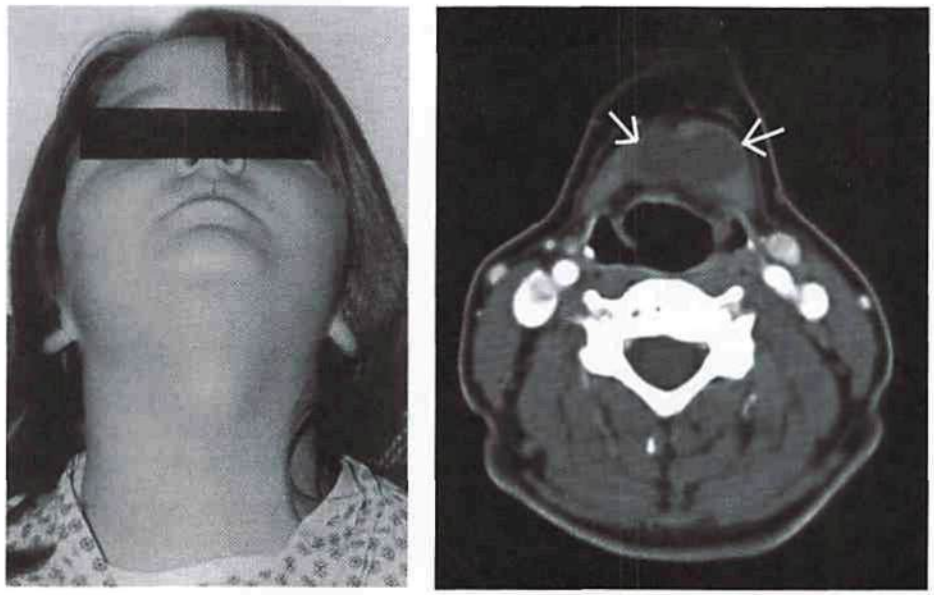
A **goiter** is an enlarged thyroid gland due to inflammation, tumor, or autoimmune disease. Endemic goiter, caused by iodine deficiency, is the most common cause of goiter worldwide.

FLASH FORWARD

A **thyroglossal duct cyst** develops when the thyroglossal duct does not close, persisting in the midline near the hyoid bone or at the base of the tongue (see Figure 2-11). **Ectopic thyroid tissue** is most commonly found at the base of the tongue.

FLASH FORWARD

Thyroid hormone deficiency during fetal development may be due to a failure of thyroid gland formation, inability to synthesize hormone (T_3/T_4), or a lack of iodine, which is essential for hormone synthesis. This condition, known as **congenital hypothyroidism** or **cretinism**, is manifest by abnormal growth and mental retardation.



A B

FIGURE 2-11. (A) Clinical appearance of a thyroglossal duct cyst. (B) Axial neck CT scan of thyroglossal duct cyst. (Part A reproduced, with permission, from Tintinalli JE, et al, *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 6th ed, New York: McGraw-Hill, 2004: 1499. Part B reproduced, with permission, from Lalwani AK, *Current Diagnosis and Treatment in Otolaryngology—Head and Neck Surgery*. New York: McGraw-Hill, 2004: 401.)

FLASH FORWARD

Medullary carcinoma of the thyroid arises from abnormal proliferation of parafollicular cells within a characteristic amyloid stroma. It is a component of the multiple endocrine neoplasia (MEN) syndrome types 1 and 2.

- The apical membranes of follicular cells face a lumen filled with a secretory substance referred to as colloid. The major constituent of colloid is the glycoprotein **thyroglobulin**, which serves as a storage form of the thyroid hormones (see Figure 2-12).
- Interspersed within the walls of thyroid follicles are small collections of parafollicular C cells that synthesize and secrete calcitonin.

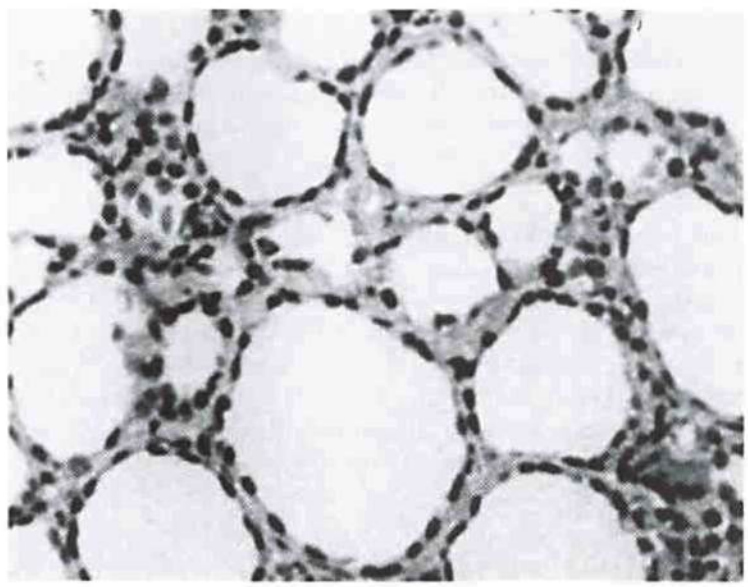


FIGURE 2-12. Thyroid follicular cells. (Reproduced, with permission, from Brunicardi FC, et al, *Schwartz's Principles of Surgery*, 8th ed, New York: McGraw-Hill, 2005: 1404.)

Thyroid Hormone Synthesis

Iodide Extraction

The thyroid acquires iodide from the circulation, providing a necessary factor for hormone synthesis.

- Follicular cells possess **iodide transporters** (sodium-iodide symporter) on their basal surfaces that **actively transport** iodide out of the blood and into the cytosol of follicular cells. This process of intracellular accumulation is known as **iodide trapping** (see Figure 2-13).
- Intracellular iodide rapidly diffuses across the apical membranes of follicular cells and into the colloidal lumen. Here it iodinates tyrosine residues on thyroglobulin.
- TSH facilitates iodide transport. Bromide, thiocyanate, and perchlorate inhibit this process.

Thyroglobulin Synthesis and Secretion

Thyroglobulin is a large glycoprotein produced by the thyroid that plays an important role in thyroid hormone synthesis.

- Thyroglobulin is synthesized by thyroid follicular cells and is secreted across the apical membrane.
- Within the follicular lumen, thyroglobulin is the principal component of colloid.

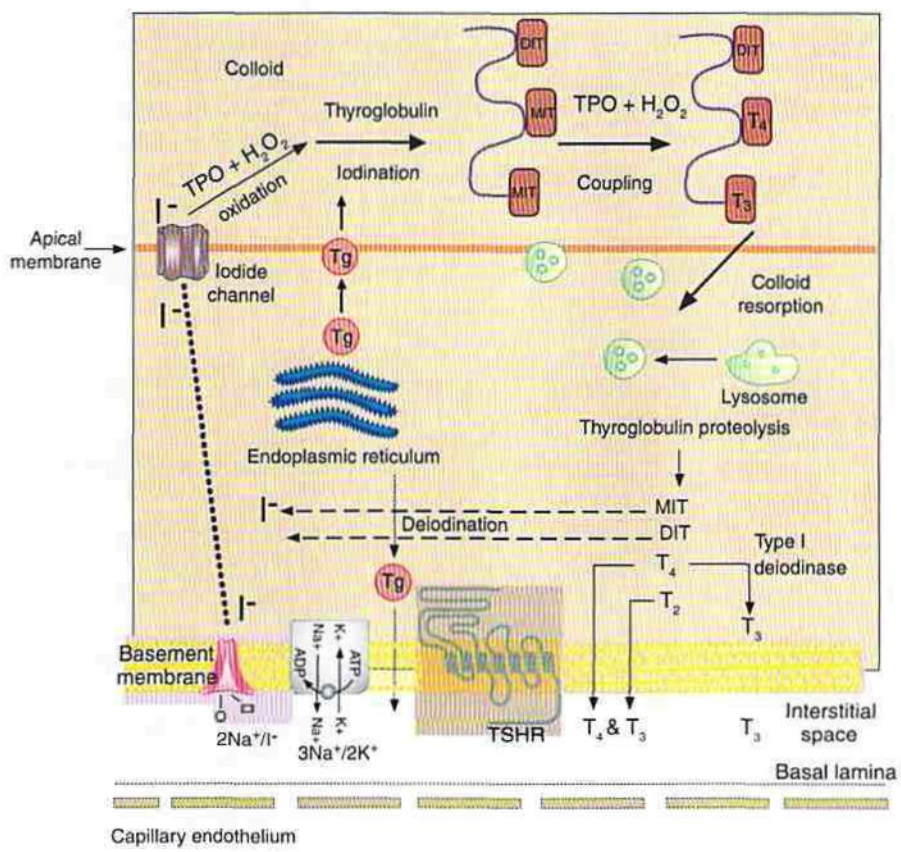


FIGURE 2-13. Thyroid hormone biosynthesis. DIT = diiodotyrosine; MIT = monoiodotyrosine; TG = thyroglobulin; TPO = thyroid peroxidase. TSHR = thyroid-stimulating hormone receptor. (Modified, with permission, from Molina PE, *Lange Endocrine Physiology*, 2nd ed, York: McGraw-Hill, 2006: 78.)

- Thyroid hormones are synthesized from tyrosine residues in the protein structure of thyroglobulin.
- Thyroglobulin serves as both a precursor and a storage form of thyroid hormone.

Oxidation and Organification

Following thyroglobulin synthesis and iodide uptake, the next step in thyroid hormone synthesis is iodination of thyroglobulin, a process that requires oxidation and organification reactions.

- Iodination of thyroglobulin is catalyzed by **thyroid peroxidase**, an enzyme located in the apical membrane of follicular cells.
- Thyroid peroxidase binds an iodide atom and a tyrosine moiety, brings them into close apposition, and promotes **oxidation** of iodide and tyrosine. This leads to the generation of short-lived free radicals that enable the reaction between iodide and tyrosine residues on thyroglobulin.
- In the process of **organification**, these free radicals (i.e., iodine and tyrosine moieties) undergo an additional reaction to form monoiodotyrosine (MIT).
- A second iodide organification reaction can take place, adding iodine to an MIT molecule to form diiodotyrosine (DIT) (see Figure 2-13).

FLASH FORWARD

Hyperthyroid patients are often treated with propylthiouracil (PTU), which inhibits the peroxidase enzyme, thereby decreasing thyroid hormone synthesis at oxidation.

Coupling

The final step in thyroid hormone synthesis is the coupling of two iodotyrosine residues (MIT or DIT) to form iodothyronine.

- With MIT and DIT still bound to thyroglobulin, they undergo **coupling** reactions to form T_4 and T_3. The final products of coupling, T_4 and T_3, remain attached to thyroglobulin during synthesis and afterward as stored hormone awaiting TSH stimulation. Coupling, like oxidation, is performed by thyroid peroxidase.
- T_3 is formed by the addition of one MIT and one DIT moiety.
- T_4 is formed by the addition reaction of two DIT moieties.
  - T_4 makes up a majority of thyroid hormone synthesized in this process.

Thyroid Hormone Release

TSH binds to surface receptors on thyroid epithelial cells and serves as the chief stimulus for hormone release.

- TSH-mediated stimulation of the thyroid gland results in pinocytosis of luminal colloid.
  - Within the follicular cells, lysosomes fuse with pinocytic vesicles and thyroglobulin is proteolytically digested. Products of protein breakdown include T_4 and T_3, both of which are transported across the basal membrane and into the circulation.
- Continued cleavage of thyroglobulin produces a large proportion of MIT and DIT molecules within follicular cells.
- Deiodinase is the enzyme that mediates iodine moiety cleavage from MIT/DIT and recycling for future thyroid hormone synthesis.

FLASH FORWARD

Individuals with a mutated or absent thyroid deiodinase enzyme may become iodine-deficient for lack of the ability to recycle iodine.

Thyroid Hormone Transport and Metabolism

T_4 and T_3 are carried in the circulation principally bound to thyroxine-binding globulin (TBG), a protein secreted by the liver.

- **TBG** slows metabolic inactivation and urinary excretion of thyroid hormones, thereby extending their half-lives.

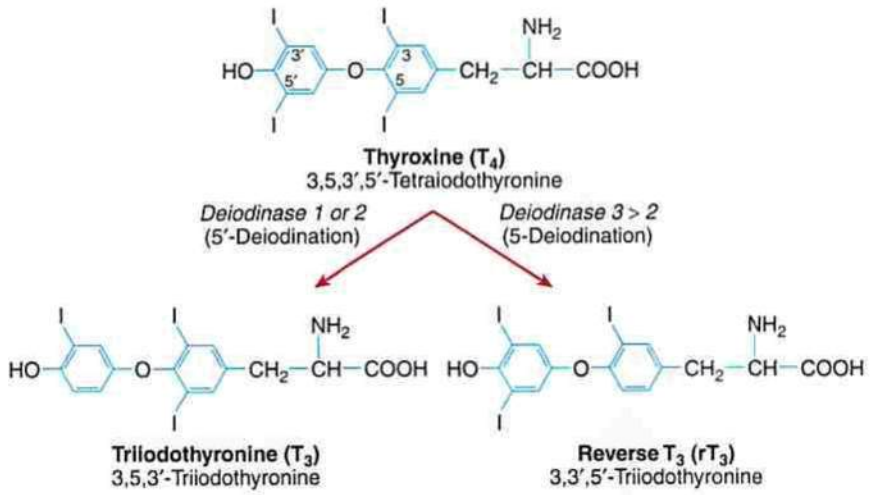


FIGURE 2-14. Thyroid hormone structure. (Modified, with permission, from Kasper DL, Braunwald E, Fauci AS, et al, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 2072.)

T_4 is the major hormone secreted by the thyroid and carried in the circulation; however, T_3 is the physiologically active form of the hormone.

- **Activation:** 5′-Deiodinase catalyzes the conversion of the prohormone T_4 to active T_3 by the removal of an iodine atom. 5′-Deiodinase is present in the liver, kidneys, thyroid, and target organs.
- **Inactivation:** A separate deiodinase enzyme targets another site on the T_4 molecule, forming biologically inactive reverse T_3 (rT_3). Enzymatic inactivation of T_3 occurs primarily in the liver and kidneys (see Figure 2-14).

Deiodination is a major mechanism by which thyroid hormone activity is enhanced or reduced, depending on whether active hormone (T_3) or inactive hormone (rT_3) is produced.

Thyroid Hormone Regulation

The hypothalamic-pituitary axis responds to changes in the levels of **free** T_4 and T_3 in the serum.

- Low levels of free thyroid hormone stimulate the release of TRH from the hypothalamus.
- TRH, in turn, enters the hypophyseal circulation and stimulates thyrotropes to release TSH into the systemic circulation (see Figure 2-15).
- TSH promotes increased thyroid hormone synthesis and secretion by upregulating the processes of iodide uptake, organification, coupling, and pinocytosis of colloid material.
- TSH also exerts trophic effects on the thyroid gland, increasing its size through continued protein synthesis.

FLASH FORWARD

In **Graves' disease**, IgG antibodies, called thyroid-stimulating immunoglobulins (TSIs), cross-react with the TSH receptor to promote thyroid gland enlargement and excessive thyroid hormone production (hyperthyroidism).

Downstream Effects

Thyroid hormone contributes to growth, development, and metabolism.

- **Bone growth:** Thyroid hormone facilitates growth by stimulating GH gene expression in somatotrophs of the anterior pituitary. Thyroid hormone also stimulates calcification and closure of cartilaginous growth plates throughout the body.
- **CNS maturation:** Thyroid hormone is vital for CNS development during the prenatal period and for the first 3 years of life. As part of normal devel-

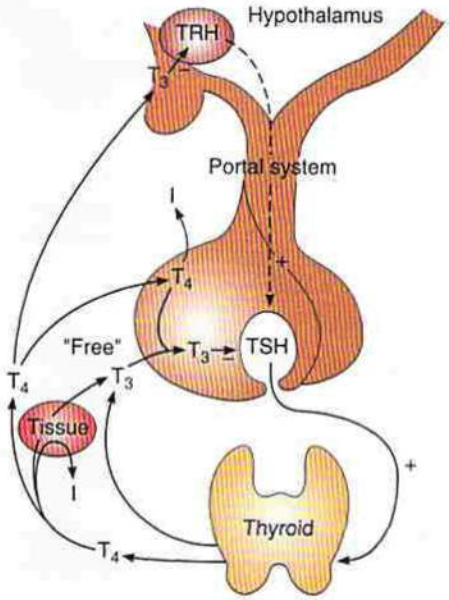


FIGURE 2-15. Hypothalamic-pituitary-thyroid axis. (Modified, with permission, from Gardner DG, Shoback D. *Greenspan's Basic & Clinical Endocrinology*, 8th ed, New York: McGraw-Hill, 2007: 232.)

FLASH FORWARD

Thyroid storm is a life-threatening form of thyrotoxicosis characterized by fever, tachycardia, psychosis, confusion, and GI symptoms. It is managed with IV fluids, PTU, and β-adrenergic blockers.

opment, neuroblasts proliferate into the second trimester, after which they begin to differentiate into neurons. Thyroid hormone promotes this transition from neuroblast division to neuronal differentiation and ultimately synapse formation.

- **Adrenergic effects:** Thyroid hormone renders β_1-adrenergic receptors in the heart more responsive to signaling molecules. Contractility, stroke volume, and heart rate are all increased, thereby augmenting cardiac output.
- **Basal metabolic rate (BMR):** Thyroid hormone promotes the synthesis of cytochromes, cytochrome oxidase, and Na^+–K^+ ATPase, while also increasing the number and activity of mitochondria. These actions ultimately increase O_2 consumption, the BMR, and body temperature.
- **Intermediary metabolism:** Thyroid hormone stimulates fuel mobilization and catabolism to support the body's increased BMR. Gluconeogenesis, glycogenolysis, and lipolysis are all enhanced to this end.

MNEMONIC

T_3 functions–4 Bs:

Brain maturation
Bone growth
Beta-adrenergic effects
Basal metabolic rate increases

KEY FACT

Thyroid hormone is absolutely essential during the perinatal period; a deficiency results in irreversible mental retardation.

Alterations in the level of thyroid hormones can have effects on several organs (see Table 2-13).

DISORDERS OF THE THYROID

Hyperthyroidism

Sixty percent of cases of hyperthyroidism are caused by Graves' disease. The remaining 40% is due to miscellaneous causes, including thyroiditis, toxic adenomas, TSH-secreting pituitary tumors, struma ovarii, and hCG-secreting tumors. See Table 2-14 for etiologies and presentations.

KEY FACT

TBG can alter the **total** levels of T_3 and T_4, but not change free, active T_3, and T_4 levels. Thus patients are euthyroid and do not show signs of hypo- or hyperthyroidism.

PRESENTATION

- Tremor, weight loss despite good appetite, irritability, restlessness, insomnia, heat intolerance, increased frequency of bowel movements or frank diarrhea, and palpitations.
- Ophthalmologic signs include a wide stare and lid lag.

TABLE 2-13. Signs and Symptoms of Abnormal Thyroid Hormone Levels

	HYPERTHYROIDISM	HYPOTHYROIDISM
Symptoms	Hyperactivity, irritability	Difficulty concentrating, poor memory
	Heat intolerance, sweating	Cold intolerance
	Palpitations	Dyspnea
	Fatigue, weakness	Fatigue, weakness
	Diarrhea	Constipation
	Polyuria	Hair loss, dry skin
	Oligomenorrhea, loss of libido	Menorrhagia
	Weight loss	Weight gain, poor appetite
		Paresthesias
		Impaired hearing, hoarse voice
Signs	Tachycardia	Bradycardia
	Tremor	Delayed tendon reflex relaxation
	Goiter	Peripheral edema
	Warm, moist skin	Dry, coarse skin
	Proximal muscle weakness	Puffy face, hands, and feet (myxedema)
	Lid retraction, lid lag	Diffuse alopecia
	Gynecomastia	Carpal tunnel syndrome

- Warm and moist skin due to peripheral vasodilatation and excessive sweating.
- Increased risk of atrial fibrillation and isolated systolic hypertension.

DIAGNOSIS

- Increased T_3 and T_4
- Decreased TSH (except in TSH-secreting tumors)

TABLE 2-14. Causes of Hyperthyroidism

CAUSE	ETIOLOGY	CLINICAL MANIFESTATIONS
Graves' disease	▪ Thyroid-stimulating immunoglobulin (TSI) binds TSH receptor on thyroid gland → ↑ T_3/T_4 (diffuse uptake on thyroid scan). ▪ Associated with other autoimmune disorders.	▪ Diffuse nontender goiter with bruit. ▪ Infiltrative ophthalmopathy (proptosis, extraocular muscle dysfunction). ▪ Pretibial myxedema.
Plummer's disease (toxic multinodular goiter)	▪ Hyperfunctioning areas that make ↑ T_3/T_4 (patchy uptake on thyroid scan). ▪ Not linked to circulating thyroid stimulators or ophthalmopathy. ▪ More common in the elderly.	▪ Less severe than Graves' disease. ▪ Associated with life-threatening arrhythmias and CHF.
Subacute thyroiditis (de Quervain's thyroiditis)	▪ Inflammation of thyroid gland → spilling of thyroid hormones → **transient hyperthyroidism** → returns to normal. ▪ Usually preceded by upper respiratory infection.	▪ Thyroid gland firm, painful, **tender.** ▪ **Fever.** ▪ **Increased ESR.** ▪ Pain radiating to ears, neck, and arm.

- Anti-TSH receptor antibodies for Graves' disease
- Radioactive iodine uptake (RAIU) scan: Localized uptake (toxic adenoma, multinodular thyroid), generalized uptake (Graves' disease), or no uptake (thyroiditis, struma ovarii)

Treatment

- β-Blockers such as propranolol: Control of adrenergic symptoms (sweating, tachycardia, tremor).
- PTU and methimazole: Inhibit thyroid hormone synthesis; PTU also inhibits the conversion of $T_4 \rightarrow T_3$.
- Radioactive iodine or surgery: To ablate thyroid function. Radioiodine is contraindicated for treatment of hyperthyroidism during pregnancy because it can cross the placenta and destroy the infant's thyroid gland, leading to hypothyroidism and its sequelae.

Hypothyroidism

Over 95% of cases of hypothyroidism result from failure of the thyroid gland itself (primary hypothyroidism). Causes of primary hypothyroidism include **Hashimoto's thyroiditis** (characterized by **anti-microsomal antibodies** and lymphocytic infiltration), **Riedel's thyroiditis** (fibrous replacement of thyroid tissue), iodine deficiency, and surgical destruction. Secondary causes of hypothyroidism include failure of the pituitary (secondary hypothyroidism) or hypothalamus (tertiary hypothyroidism).

Presentation

- Lethargy, fatigue, muscle weakness.
- Cold intolerance, constipation, weight gain.
- Delayed recovery of deep tendon reflexes.
- Slow mentation.
- Diastolic hypotension.
- Loss of lateral one-third of eyebrows, coarse/dry skin, deep voice.
- In newborns, hypothyroidism causes cretinism (mental retardation, short stature, coarse features, umbilical hernia).
- **Myxedema coma:** Stupor, coma, seizures, and hypoventilation. A life-threatening hypothyroid condition that results from long-standing, untreated hypothyroidism. Triggered by trauma, infections, and cold exposure.

Diagnosis

- T_3/T_4/TSH/TRH: May be helpful to diagnose and distinguish among primary, secondary, and tertiary causes.
- Chemistries: Mild normocytic anemia, hyponatremia, hypoglycemia.
- Immunology: Antimicrosomal antibody test for Hashimoto's thyroiditis.
- Imaging: Pituitary and hypothalamus for tumor.

Treatment

Hypothyroidism is treated with **levothyroxine** (T_4) replacement. For myxedema coma, empiric adrenal replacement therapy is used as well.

Thyroid Neoplasms

Thyroid cancer is the most common endocrine malignancy in the United States with an annual incidence of approximately 2 cases per 100,000. Risk factors include previous childhood head and neck radiation exposure, sex (a high percentage of nodules are malignant in men), age (a high percent-

TABLE 2-15. Types of Thyroid Cancer

Type	Prevalence	Characteristics	Treatment
Papillary carcinoma	70%–80%	▪ History of radiation exposure increases risk. ▪ Slow-growing, spreads by lymphatics in the neck. ▪ "Orphan Annie" nuclei (cells in papillary cancer have dispersed chromatin, giving appearance of empty nuclei). ▪ Psammoma bodies (concentric calcification of individual necrotic tumor cells).	Lobectomy or total thyroidectomy ± radioiodine
Follicular carcinoma	10%–20%	▪ More aggressive than papillary carcinomas. ▪ Tends to invade into blood vessels → spreads to bone, lung, and liver (lymph node involvement rare).	Total thyroidectomy + postoperative iodine ablation
Medullary carcinoma	5%	▪ Arises from parafollicular cells of thyroid. ▪ Produces calcitonin (can be used as tumor marker). ▪ Amyloid deposits (derived from altered calcitonin molecules). ▪ Associated with the MEN 2A and MEN 2B syndromes.	Total thyroidectomy
Anaplastic carcinoma	5%	▪ Highly aggressive. ▪ Poor prognosis (death within a few months).	Chemotherapy and radiation

age of nodules are malignant in the young), and family history (MEN 2A/2B syndromes).

Presentation

Typically presents as a solitary nodule. Dyspnea, coughing/choking spells, dysphagia, and hoarseness may occur due to compression of the trachea or esophagus.

Diagnosis

- Chemistries: TSH
- Radioactive iodine thyroid scintiscanning (RAIU): Cold nodule without uptake suggests need for biopsy. Hot nodules are usually benign adenomas.
- Fine-needle aspiration: Fifteen percent are suspicious or malignant, and most biopsies are benign or indeterminate. Provides histologic diagnosis of four varieties of cancer (see Table 2-15).

Treatment

Ablation or medical therapy for benign nodules. Surgery for all cancers except anaplastic.

DRUGS FOR HYPOTHYROIDISM

L-thyroxine (T_4) and liothyronine (T_3) are the natural hormones made by the thyroid gland. Levothyroxine (T_4) is the principal pharmacologic agent used for hypothyroidism. Liothyronine is not used routinely for the treatment of hypothyroidism because it can precipitate heart failure; it is used mainly in myxedema coma.

Levothyroxine

Mechanism

T_4 analog, binds to nuclear receptors. Leads to increased protein synthesis, increased metabolic rate, and increased β-receptors → increased sensitivity to catecholamines.

Uses

Hypothyroidism.

Side Effects

Signs and symptoms of hyperthyroidism (i.e., tachycardia, heart failure, sweating, tremor, diarrhea).

ANTITHYROID DRUGS

There are two main classes of drugs used to treat hyperthyroidism: Thionamides and iodine. Thionamides inhibit thyroid hormone synthesis. Excess iodine reduces thyroid synthesis paradoxically, and radioiodine destroys cells that make thyroid hormone.

Thionamides (Methimazole, Propylthiouracil)

Mechanism

Inhibits oxidation and organification of iodine, a step required in thyroid hormone synthesis; PTU also inhibits peripheral conversion of T_4 to T_3.

Uses

Hyperthyroidism; PTU is the treatment of choice during breast-feeding because little PTU passes into breast milk.

Side Effects

Rash, urticaria, fever, nausea; major effects include agranulocytosis, thrombocytopenia, acute hepatic necrosis, and vasculitis.

Contraindication

Both methimazole and PTU cross the placenta and should be avoided during pregnancy.

Iodine (Iodide and Radioiodine)

Mechanism

Iodide is selectively concentrated in the thyroid gland for hormone synthesis. Radioiodine (I^{131}) is also concentrated in the thyroid gland, and emits beta and gamma radiation.

Uses

Large doses of iodine are used for thyroid storm and before thyroidectomy (to make the gland less vascular). Used also for hyperthyroidism and adjunctive treatment for some thyroid cancers.

Side Effects

Metallic taste, excessive salivation, diarrhea, rash.

PARATHYROID GLAND

The parathyroid glands play an important role in calcium homeostasis and bone health, predominantly through involvement in calcium and phosphate metabolism.

- The main hormone that mediates these effects is parathyroid hormone (PTH), which acts on the kidneys and bone. PTH increases serum calcium while decreasing serum phosphate concentrations.
- PTH is not the only mechanism by which the body regulates serum calcium and phosphate levels. Vitamin D also plays an important role.
- **Vitamin D** increases intestinal absorption of calcium and phosphate and, together with PTH, promotes bone resorption, resulting in elevated levels of calcium and phosphate.

Anatomy

The parathyroid glands are four small, pea-sized structures attached to the posterior aspect of the thyroid gland, external to the fibrous thyroid capsule (see Figure 2-16). The glands are anatomically separated into two superior and two inferior parathyroids. Both sets are supplied by the inferior thyroid arteries with venous drainage through the thyroid plexus of veins.

Embryology

The parathyroid glands are derived from pharyngeal (branchial) pouch endoderm. Four pharyngeal pouches exist during development, with each contributing to the formation of important structures of the head and neck (see Tables 2-16 through 2-18 for an overview of pharyngeal pouches, clefts, and arches). Each pouch represents an evagination of endodermal tissue within the foregut.

- Differentiation of the third branchial pouch takes place in the fifth and sixth weeks of gestation.
  - The ventral wing of the third pouch gives rise to the thymus.
  - The dorsal wing ultimately becomes the inferior parathyroids.

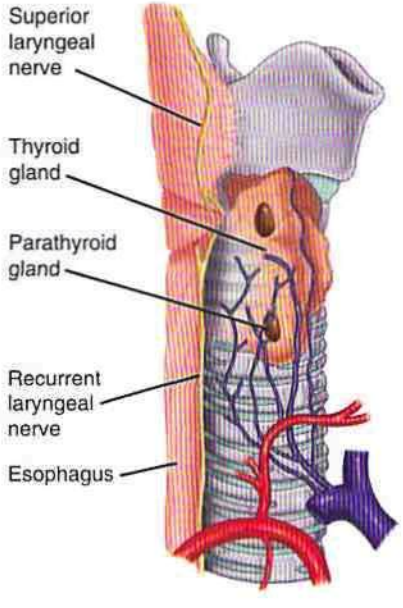


FIGURE 2-16. Lateral view of trachea, thyroid gland, and parathyroids.

TABLE 2-16. Branchial Pouch Derivatives

Branchial Pouch	Derivatives
First pouch	Middle ear cavity, eustachian tube, mastoid air cells.
Second pouch	Epithelial lining of palatine tonsil.
Third pouch (dorsal wing)	Inferior parathyroids.
Third pouch (ventral wing)	Thymus.
Fourth pouch	Superior parathyroids, thyroid gland C cells (derived from ultimobranchial body).

TABLE 2-17. Pharyngeal Clefts and Membranes

Branchial Cleft	Derivatives
First cleft	External auditory meatus
Second, third, and fourth clefts	Temporary cervical sinuses (normally obliterated)
Branchial Membrane	**Derivatives**
First membrane	Tympanic membrane
Second, third, and fourth membranes	Temporary structures (normally obliterated)

TABLE 2-18. Branchial Arches

Branchial Arch	Derivatives (Cartilage)	Derivatives (Muscle)	Innervation
1	Mandible, malleolus, incus, spheno-mandibular ligament	Temporalis, masseter, lateral/medial pterygoids, mylohyoid, anterior belly of the digastric, tensor tympani, tensor veli palati, anterior two-thirds of the tongue.	CN V2 and V3
2	Stapes, styloid process, lesser horn of the hyoid, stylohyoid ligament	Stapedius, stylohyoid, posterior belly of the digastric, muscles of facial expression.	CN VII
3	Greater horn of the hyoid	Stylopharyngeus.	CN IX
4	Thyroid, cricoid, arytenoids, corniculate, cuneiform	Cricothyroid, levator veli palatini, pharyngeal constrictors.	CN X (superior laryngeal branch)
5	No major developmental contributions		
6	Thyroid, cricoid, arytenoids, corniculate, cuneiform	All intrinsic muscles of larynx except the cricothyroid.	CN X (recurrent laryngeal branch)

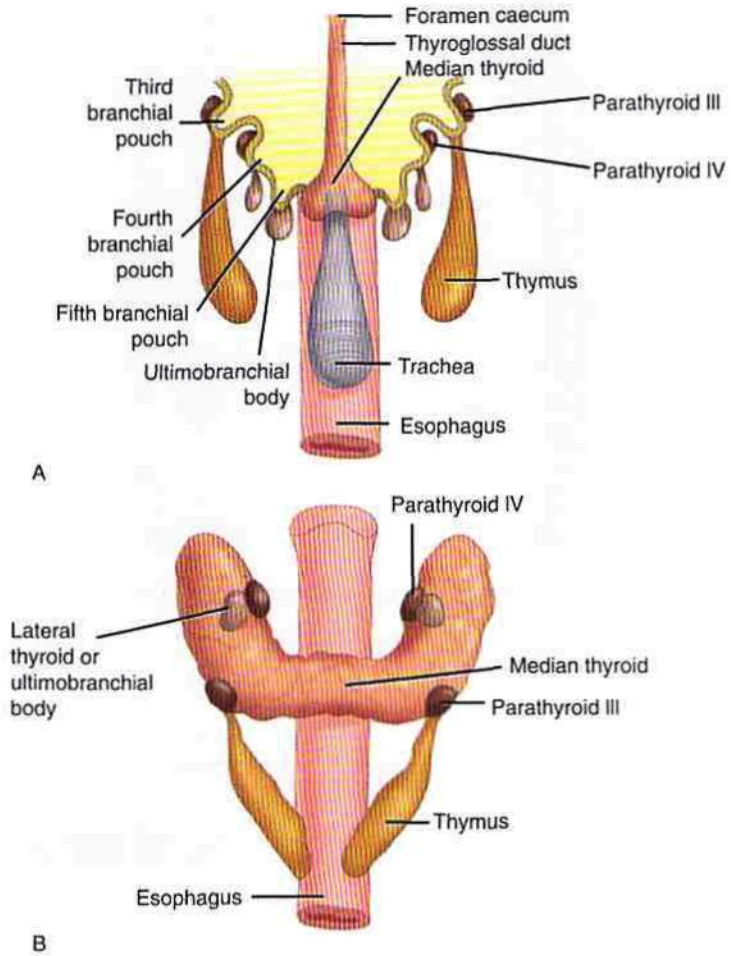


FIGURE 2-17. Parathyroid embryology. (A) Schematic of branchial pouches with associated derivatives. (B) Migration of the inferior parathyroids.

- By the seventh week of gestation, the third branchial pouch diverticulum elongates, ultimately allowing the developing thymus and inferior parathyroids to separate from the pharynx (see Figure 2-17).
  - The thymus migrates medially and caudally, pulling the inferior parathyroids until the thymus and parathyroids lose their connections to one another.
  - The inferior parathyroids ultimately attach to the dorsal surface of the thyroid.
- The fourth branchial pouch, which gives rise to the superior parathyroids, follows a similar developmental course and timeline.
  - The developing superior parathyroids do not migrate with another structure (i.e., thymus), but rather travel a shorter distance before attaching to the dorsal surface of the thyroid.

Histology

The parathyroid glands are connective tissue–encapsulated structures that contain two populations of cells: **chief cells** and **oxyphil cells**.

- Chief cells are predominant. They are small, polygonal cells with secretory granules containing PTH.
  - Chief cells are arranged into curvilinear cords separated by capillaries (see Figure 2-18).

KEY FACT

The inferior parathyroids are derived from the third branchial pouch, whereas the superior parathyroids are derived from the fourth branchial pouch, an apparent reversal of the rostro-caudal arrangement of structures during development. This is due to the paired migration of the inferior parathyroids with the thymus, which facilitates enhanced caudal migration.

FLASH FORWARD

Accessory parathyroid glands are present in approximately 13% of the general population. They likely result from fragmentation of the tissue during migration.

FLASH FORWARD

Ectopic parathyroid tissue results from abnormal migration. Ectopic parathyroids can be found in the anterior/posterior mediastinum, retroesophageal space, or even within the thyroid or thymus. Despite migration, the parathyroids typically remain symmetrical from side to side.

FLASH FORWARD

Branchial cysts result from failed obliteration of the temporary cervical sinuses, producing a persistent cyst in the neck.

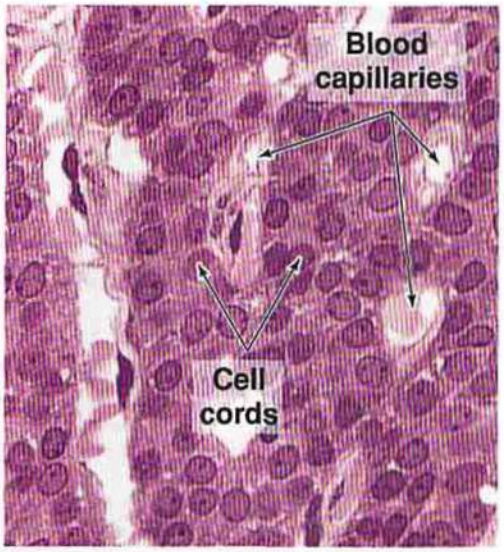


FIGURE 2-18. Section of parathyroid gland demonstrating chief cells arranged in cords separated by capillaries. (Reproduced, with permission, from Junqueira LC, Carneiro J, *Basic Histology: Text & Atlas*, 11th ed, New York: McGraw-Hill, 2005: 416.)

FLASH FORWARD

DiGeorge's syndrome is a consequence of abnormal development of pharyngeal pouches 3 and 4. Clinical manifestations include hypocalcemia secondary to absence of the parathyroid glands, immune deficiency secondary to absence of thymic tissue leading to abnormal T-cell maturation, and congenital cardiac malformations.

- Oxyphil cells are large cells containing abundant acidophilic mitochondria, and have an unknown function.

CALCIUM AND PHOSPHATE HOMEOSTASIS

Calcium plays an important role in a host of physiologic processes, ranging from muscle contraction to neuronal impulse transmission. Extracellular calcium concentrations are tightly regulated against large fluctuations. Despite its importance, only 0.1% of total body calcium is found in the ECF. The vast majority of the remaining calcium, approximately 99%, is stored within bone (see Figure 2-19).

- Fifty percent of serum calcium is bound to plasma proteins.
- Ten percent of serum calcium is complexed with anions such as phosphate and citrate.
- Forty percent of serum calcium is in a free, ionized form.

Only free calcium is biologically active.

Calcium and phosphate homeostasis are regulated through the coordinated actions of three hormones: PTH, vitamin D, and calcitonin. These hormones control calcium and phosphate by acting on bone, intestine, and kidney.

Parathyroid Hormone

PTH is a polypeptide hormone synthesized and secreted by the parathyroid chief cells.

PTH is initially synthesized as a larger, inactive preprohormone. Proteolytic processing produces a final active hormone that is stored in secretory granules of chief cells. The secreted form of the hormone contains 84 amino acids.

FLASH FORWARD

First arch syndromes are a collection of facial malformations resulting from abnormal migration of neural crest cells into pharyngeal arch 1. **Pierre Robin syndrome** (Pierre Robin sequence) is characterized by micrognathia, glossoptosis (the tongue falls back and downward), and cleft soft palate.

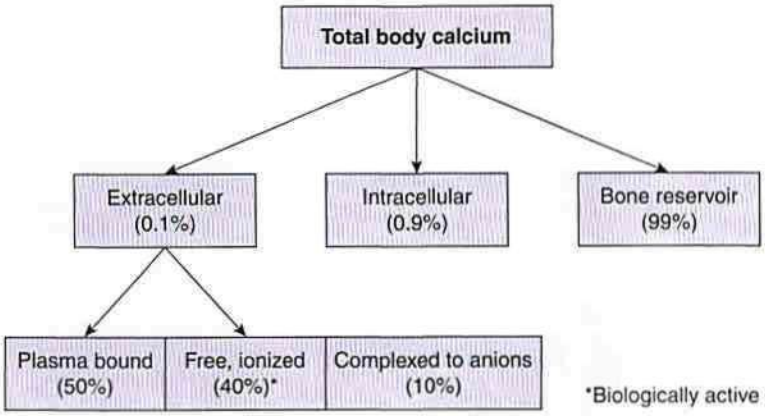


FIGURE 2-19. Distribution of total body calcium. Like calcium, phosphate is involved in a range of physiologic processes. A very small quantity (1%) of total body phosphate is found in the extracellular space; most phosphate is in bone.

Despite rapid metabolism of PTH by the kidneys after secretion, smaller peptide fragments of the hormone retain full biological activity for hours.

PTH Regulation

The stimuli for PTH release include serum calcium and magnesium levels.

- PTH secretion is inversely proportional to serum ionized calcium levels. Depressed serum calcium stimulates increased PTH secretion, whereas high serum calcium levels inhibit secretion.
- Reductions in serum magnesium also affect PTH secretion. Mild decreases in magnesium stimulate PTH secretion. Severe hypomagnesemia, however, inhibits PTH secretion.

Mechanisms of Action

In order to affect serum calcium and phosphate levels, PTH alters bone turnover, renal tubule reabsorption, and vitamin D activation. PTH is also responsible for raising serum calcium levels and decreasing serum phosphate levels. It does so through indirect actions at the level of the intestine and direct effects on the kidneys and bone (see Figure 2-20). These actions include:

- **Increased bone resorption:** PTH stimulates both osteoclasts and osteoblasts (bone resorption > bone formation), leading to increased calcium and phosphate levels.
  - PTH enhances the activity of existing osteoclasts and also promotes the formation of new osteoclasts.
  - Increased resorption from bone mineral leads to the release of both calcium and phosphate into the extracellular space.
- **Increased renal calcium reabsorption:** PTH works on the proximal and distal renal tubules. It stimulates the distal tubule to increase reabsorption of calcium, effectively raising serum calcium levels.
- **Increased phosphate excretion:** In the proximal renal tubule, PTH inhibits phosphate reabsorption, leading to enhanced phosphate excretion.
  - The reduction in serum phosphate reduces the quantity of complexed calcium in the circulation (phosphate and calcium bind in serum), thereby raising the amount of extracellular free calcium.

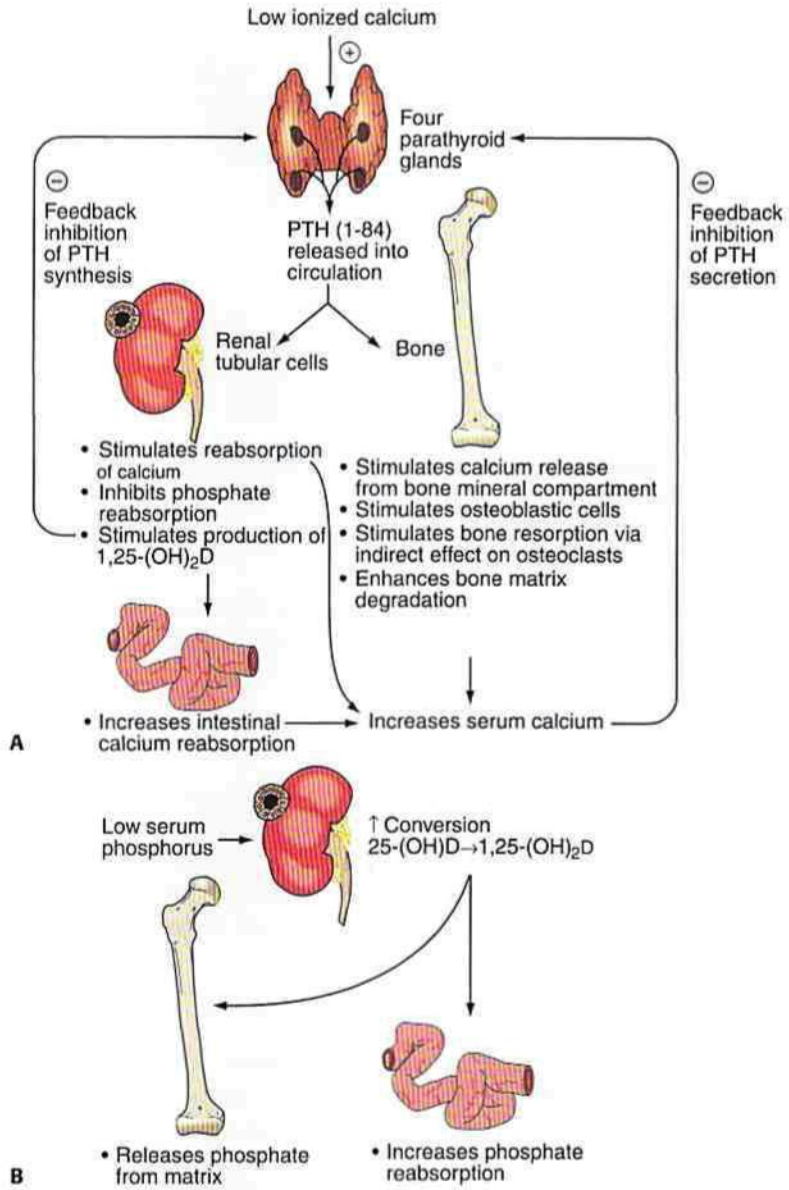


FIGURE 2-20. Actions of PTH and 1,25-(OH)2D in the maintenance of calcium (A) and phosphate (B) homeostasis.

- PTH stimulates distal tubule reabsorption of calcium expanding the free calcium pool in the circulation.

- **Increased vitamin D activity increases intestinal Ca absorption:** PTH increases the activity of 1α-hydroxylase in the kidney. This results in increased levels of 1,25-$(OH)_2$ vitamin D (calcitriol). Calcitriol affects intestinal absorption of calcium and bone resorption (see below). Thus, PTH, via its activation of vitamin D, has an indirect effect on serum calcium levels.

Vitamin D

The chief forms of vitamin D are ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3).

- Vitamin D_2 is produced by plant and fungal sources. It is not synthesized within the human body.

- Vitamin D_3 is produced by animal sources. Endogenous production also takes place in the skin. Specific wavelengths of UV light react with 7-dehydrocholesterol to produce vitamin D_3. Sun exposure prevents vitamin D deficiency.

Activation

Following synthesis in the skin, cholecalciferol (vitamin D_3) is initially inactive. It must undergo a series of addition reactions in the liver and kidney to become biologically active (see Figure 2-22).

- Cholecalciferol is first transported to the liver, where it undergoes a hydroxylation reaction to form **25-hydroxycholecalciferol**. This rate-limiting step determines the amount of active vitamin D in the circulation as opposed to the amount of inactive vitamin stored in the liver. 25-Hydroxycholecalciferol exerts negative feedback on this process in the liver.
- In the kidney, 25-hydroxycholecalciferol undergoes a second hydroxylation reaction catalyzed by **1α-hydroxylase**. The product of this reaction, **1,25-dihydroxycholecalciferol [1,25-$(OH)_2$ vitamin D]**, is the active form of vitamin D, also referred to as calcitriol. Importantly, 1α-hydroxylase activity is upregulated by PTH. In this way, PTH activity leads to vitamin D activity.
  - PTH increases 1,25-$(OH)_2$ vitamin D formation.
  - Low calcium increases 1,25-$(OH)_2$ vitamin D formation.
  - Low phosphate increases 1,25-$(OH)_2$ vitamin D formation.

Actions

The active form of vitamin D (calcitriol) raises extracellular levels of calcium and phosphate and promotes the mineralization of bone. These metabolic changes are the result of effects on the intestine, kidneys, and bone:

- **Increases intestinal calcium and phosphate absorption:** 1,25-$(OH)_2$ vitamin D upregulates gene transcription of a calcium-binding protein (cal-

FLASH FORWARD

Vitamin D deficiency in children causes **rickets**, which is characterized by the inability to calcify newly formed bone matrix (osteoid) with consequent malformation (bowing) of long bones (see Figure 2-21).

FLASH FORWARD

Vitamin D deficiency in adults results in **osteomalacia**, which, like rickets, is characterized by defective mineralization of bone. Osteomalacia causes pain, proximal muscle weakness, and bony deformities. It is treated with vitamin D replacement.

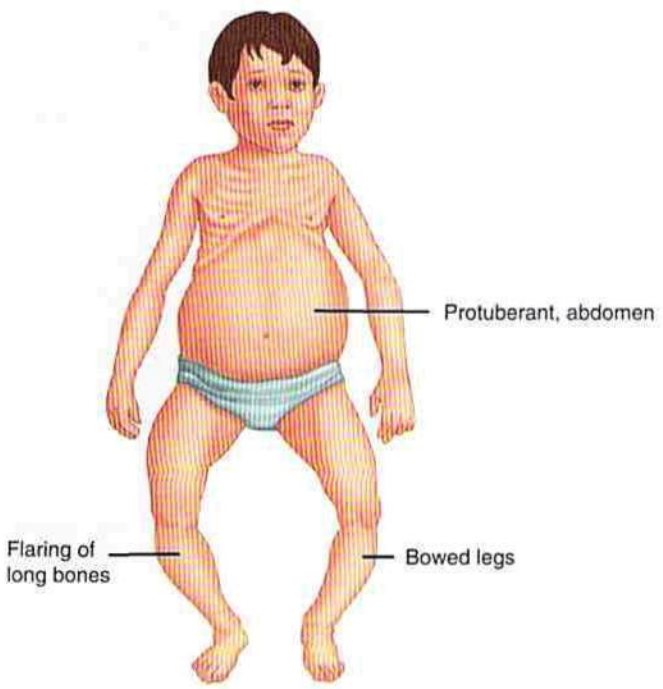


FIGURE 2-21. Clinical signs of rickets in a young boy. Note the bowed legs, protuberant abdomen, and flaring of long bones.

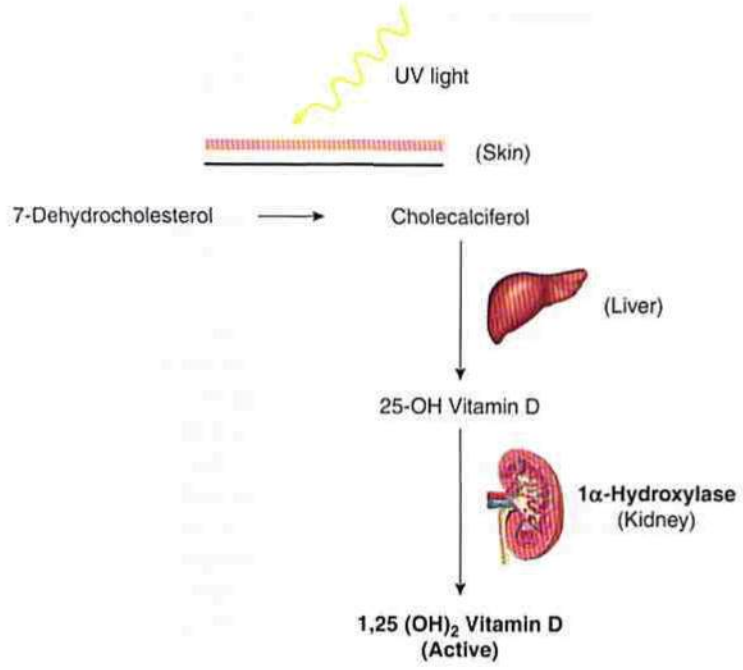


FIGURE 2-22. Activation of vitamin D.

bindin D-28K) in the intestinal brush border. This protein increases the absorption of dietary calcium.

- **Increases bone resorption of calcium and phosphate:** 1,25-$(OH)_2$ vitamin D is vital for PTH-induced bone resorption. It is thought to facilitate this process by increasing calcium transport across membranes (similar to the mechanism in the intestine). In the absence of vitamin D, PTH has limited effects on bone. Thus, at the level of bone, 1,25-$(OH)_2$ vitamin D promotes resorption of calcium and phosphate so they can be used for the mineralization of new bone.
- **Increases renal reabsorption of calcium and phosphate (minor effect):** 1,25-$(OH)_2$ vitamin D promotes increased reabsorption of both ions by the renal tubules. This effect is relatively minor and contributes little to the overall concentrations of extracellular calcium and phosphate.

Calcitonin

Calcitonin is a polypeptide secreted by the parafollicular or C cells of the thyroid gland. Although it promotes reduction in extracellular calcium through anti-PTH-like effects, calcitonin does not play a necessary, vital role in calcium homeostasis. Patients who have had their thyroid removed (e.g., as treatment for thyroid cancer) show no changes in serum calcium concentrations despite the complete absence of calcitonin.

Actions

Calcitonin is secreted in response to high serum calcium levels. It acts primarily on bone, decreasing the resorptive activity of osteoclasts. Calcitonin also has mild and inconsequential effects on the intestines and renal tubules aimed at decreasing extracellular calcium.

CALCIUM DISORDERS

Primary Hyperparathyroidism

In primary hyperparathyroidism, inappropriate excess secretion of PTH causes hypercalcemia. A benign parathyroid adenoma is responsible for 80% of cases, while parathyroid gland hyperplasia accounts for the remaining 20% of cases.

Presentation

Usually asymptomatic. Incidentally discovered based on elevated calcium levels. When symptomatic, presents with renal, GI, or neurologic symptoms.

- Renal: Polyuria, hypercalcinuria, renal stones (calcium oxalate stones). If chronic, can lead to nephrocalcinosis and eventually renal failure.
- Skeletal: Bone pain and aches. Increased PTH leads to increased osteoclastic activity → increased bone resorption and osteopenia.
- GI: Nausea, vomiting, weight loss, constipation, anorexia, peptic ulcer disease, acute pancreatitis.
- Neurologic: Mental status changes, depression, fatigue.

In hypercalcemic crisis: Polyuria, dehydration, mental status changes.

Diagnosis

- CBC: Increased Ca^{2+}, decreased phosphate; chloride is often elevated.
- Also check PTH-related peptide (PTHrP), vitamin D levels, alkaline phosphatase, urine calcium.
- **Endocrine:** Increased PTH.
- ECG: Short QT interval.

Treatment

- First-line treatment is surgical exploration and partial or total parathyroidectomy.
- Medical treatment includes increased fluid intake (4–6 L normal saline per day) and oral phosphates. Can give diuretics (furosemide) to enhance calcium excretion. Can also give bisphosphonates to inhibit bone loss, or calcitonin or glucocorticoids.

Other Causes of Hypercalcemia

- **Malignancy-induced hypercalcemia** can result from bone metastasis (e.g., breast cancer) or tumors that produce PTHrP, including squamous cell carcinoma of the lung and renal adenocarcinoma.
- **Vitamin D toxicity** secondary to sarcoid, TB, or histoplasmosis. For example, in **sarcoidosis**, lymphocytes in granulomas make 1α-hydroxylase → increased vitamin D → increased calcium resorption.
- **Familial hypocalciuric hypercalcemia** (FHH): Autosomal-dominant disorder caused by a mutation in calcium receptors → leads to inappropriate secretion of PTH → increased calcium resorption. Although hypercalcemia is a main feature of this disease, urinary calculi and renal failure are rare.
- **Thiazide diuretics.**
- **Milk-alkali syndrome:** Ingestion of excessive amounts of calcium-based antacids.

Primary Hypoparathyroidism

Causes in order of most to least common: Hypoparathyroidism following thyroid surgery, in which the surgeon accidentally removes the parathyroid

KEY FACT

Renal failure patients with secondary parahyperthyroidism may develop bony lesions and cystic demineralization. This condition, **osteitis fibrosa cystica**, occurs when the bone's normal cellular and marrow elements are replaced by fibrous tissues.

MNEMONIC

Patients with hypercalcemia: "Stones, bones, groans, and psychiatric overtones."

MNEMONIC

***Causes for hypercalcemia:* MISHAP**

Malignancy, milk-alkali syndrome
Intoxication with vitamin D
Sarcoidosis
Hyperparathyroidism
Alkali
Paget's disease

KEY FACT

In the case of parathyroid hyperplasia, the surgeon removes three of the four parathyroid glands, and then auto-transplants (reimplants) the piece of remnant parathyroid into the patient's forearm to serve as the sole source of PTH.

glands, pseudohypoparathyroidism due to PTH end-organ resistance, and **DiGeorge's syndrome** (failure of the third and fourth pharyngeal pouches to develop).

Presentation

Neuromuscular excitability due to hypocalcemia.

- Muscle fatigue and weakness.
- Numbness and tingling around the mouth, hands, and feet.
- Tetany: **Chvostek's sign** (tapping of the facial nerve in front of the ear → upper lip and facial muscles contract); **Trousseau's sign** (inflation of a BP cuff to a pressure higher than systolic BP → carpal spasms).
- Laryngeal spasm.
- Basal ganglia calcifications (can cause parkinsonian symptoms). The ocular lens can also be calcified, leading to cataracts.
- Depression, psychosis.

Diagnosis

- **CBC, endocrine:** Decreased PTH → decreased Ca, increased phosphate. Check albumin, vitamin D, Mg, alkaline phosphatase, and urine calcium as well. See Table 2-19 for lab differential of hypocalcemia.
- **ECG:** Increased QT interval.
- **Imaging:** Basal ganglia calcifications.

Treatment

Calcium supplements, vitamin D supplements (calcitriol), and IV calcium gluconate for acute symptoms.

Other Causes of Hypocalcemia

- **Pseudohypoparathyroidism:** End-organ resistance to PTH (kidney and bones do not respond to PTH). Patients may have **Albright's hereditary osteodystrophy**, characterized by short stature, shortening of the fourth and fifth metacarpals, and mild mental retardation.
- **Pseudopseudohypoparathyroidism.**
- **Hypoalbuminemia** causes a decrease in **total** calcium, but ionized calcium levels are normal. There are no clinical signs of calcium deficiency.
- **Hypomagnesemia** leads to decreased PTH synthesis and release.
- **Acute pancreatitis:** Enzymatic fat necrosis uses up calcium. Other conditions that lead to calcium sequestration include citrate excess after blood transfusions, acute increases in PO_4 due to rhabdomyolysis, tumor lysis, and ARF.

TABLE 2-19. Summary of Calcium Disorders

	Serum Calcium	Serum Phosphate	PTH
Primary hyperparathyroidism	↑	↓	↑
Malignancy-induced hypercalcemia (PTHrP)	↑	↓	↓
Primary hypoparathyroidism	↓	↑	↓
Pseudohypoparathyroidism	↓	↑	↑/normal

CALCIUM DRUGS

Bisphosphonates (e.g., Alendronate)

Mechanism

Stabilizes bony matrix, coats hydroxyapatite to prevent osteoclasts from breaking bone down.

Uses

Postmenopausal osteoporosis and in Paget's disease to reduce bone turnover.

Side Effects

Heartburn, stomach upset, joint/back pain, headache.

Calcitonin

Mechanism

Lowers serum calcium, has analgesic properties for bone pain.

Administration

Nasal spray.

Uses

Hypercalcemic states.

Side Effects

Runny rose, nasal discomfort, flushing.

Calcitriol

Mechanism

Activated form of vitamin D increases calcium absorption from kidneys.

Uses

Hypocalcemia.

Side Effects

Signs and symptoms of vitamin D intoxication include weakness, headache, somnolence, constipation, and metallic taste.

Adrenal Gland

The adrenal or suprarenal glands coordinate the body's response to stress. The gland is anatomically and functionally divided into two parts, the adrenal medulla (core) and outer adrenal cortex.

The adrenal medulla is a functional extension of the sympathetic nervous system, secreting the catecholamines epinephrine and norepinephrine into systemic circulation.

In contrast, the adrenal cortex synthesizes steroid hormones, collectively known as corticosteroids, which have diverse functions ranging from stress responses (**cortisol**) to control of water and electrolyte balance (**aldosterone**) to masculinizing effects (**testosterone**).

ANATOMY

FLASH FORWARD

Other **neural crest derivatives** include autonomic nervous system, dorsal root ganglia, cranial nerves, melanocytes, enterochromaffin cells, pia and arachnoid, celiac ganglion, Schwann cells, odontoblasts, parafollicular C cells of the thyroid, laryngeal cartilage, bones of the skull.

The triangular-shaped adrenals sit atop the superoanterior aspects of the kidneys, where they are encased in a capsule of fat and connective tissue (see Figure 2-23).

- The vascular supply to the adrenal glands consists of three sets of arteries:
  - **Superior adrenal arteries**, which are branches off the inferior phrenic artery
  - **Middle adrenal arteries**, which originate from the abdominal aorta adjacent to the superior mesenteric artery (SMA)
  - **Inferior adrenal arteries**, which are branches off the renal artery
- The venous drainage of the adrenal gland differs between the two sides.
  - Left adrenal → left adrenal vein → left renal vein → inferior vena cava (IVC)
  - Right adrenal → right adrenal vein → IVC

EMBRYOLOGY

FLASH FORWARD

Pheochromocytoma is a rare neoplasm formed from chromaffin cells at extra-adrenal sites (10%) or the adrenal medulla (90%). It is the most common tumor of the adrenal medulla in adults.

The adrenal cortex and medulla differ in terms of embryologic origins.

- **Adrenal cortex:** Derived from mesoderm.
- **Adrenal medulla:** Derived from neural crest cells, which differentiate into chromaffin cells.

HISTOLOGY

FLASH FORWARD

Neuroblastoma is a neoplasm formed from neural crest cells that may be found anywhere along the sympathetic chain, including the adrenal medulla. It is the most common tumor of the adrenal gland in children.

The adrenal cortex is further divided into three distinct layers (see Table 2-20).

- **Zona glomerulosa:** A relatively thin layer (15% of the cortex) comprised of cells containing the enzyme aldosterone synthase. Consequently, the zona glomerulosa is the only layer that is capable of producing appreciable quantities of the mineralocorticoid **aldosterone**.
- **Zona fasciculata:** The largest layer (75% of the cortex) comprised of cells that synthesize and secrete **glucocorticoids** (cortisol and corticosterone) and smaller quantities of androgens and estrogens.
- **Zona reticularis:** The deepest layer (10% of the cortex) comprised of cells that synthesize adrenal **androgens** (dehydroepiandrosterone [DHEA] and

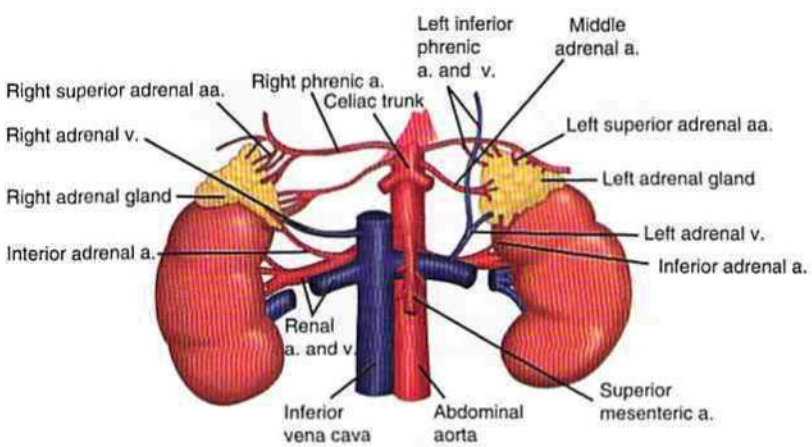


FIGURE 2-23. Anatomy and blood supply of adrenal glands. (Modified, with permission, from Brunicardi FC, et al, *Schwartz's Principles of Surgery*, 8th ed, New York: McGraw-Hill, 2005: 1450.)

TABLE 2-20. Adrenal Gland Summary

Region	Hormone	Controlled by	Loss Leads to ...
Glomerulosa	Aldosterone	Angiotensin II, potassium	Hyponatremia, hypovolemia, hyperkalemia
Fasciculata	Cortisol	ACTH	Circulatory failure, decreased ability to mobilize sugars
Reticularis	Androgens	ACTH	Little physiologic effect (major role is in prepubertal development)

androstenedione) in addition to smaller quantities of glucocorticoids and estrogens.

STEROID HORMONE SYNTHESIS

Cholesterol Acquisition

Steroid hormones of the adrenal cortex are synthesized using cholesterol as a precursor. Approximately 20% of this cholesterol is produced de novo within adrenal cortical cells; the remainder is acquired from circulating low-density lipoproteins (LDL). Internalization of LDL molecules is via endocytosis followed by hydrolysis within lysosomes to produce free cholesterol within cells.

Synthetic Pathways

Free cholesterol within adrenal cortical cells is transported to mitochondria.

- The initial step in steroid hormone synthesis is rate-limiting and conserved across all layers of adrenal cortex. In this reaction, **cholesterol desmolase** converts cholesterol to pregnenolone (see Figure 2-24). ACTH and angiotensin II stimulate this conversion.
- 3-β-Hydroxysteroid dehydrogenase and 21-hydroxylase are required for the synthesis of precursors in the pathways to both aldosterone and cortisol. 11-β-Hydroxylase is required for synthesis of cortisol.
- 17-α-Hydroxylase converts pregnenolone and progesterone into androstenedione and DHEA, respectively, both precursors of adrenal androgens.
- The ultimate products are aldosterone (zona glomerulosa), cortisol (zona fasciculata), and androgens (zona reticularis).

GLUCOCORTICOIDS

Glucocorticoid Synthesis and Regulation

The hypothalamus, anterior pituitary, and adrenal cortex interact to coordinate glucocorticoid synthesis. Hypoglycemia, trauma, illness, fever, psychological stress, and physical exertion trigger the hypothalamus to secrete CRH.

- CRH stimulates corticotrophs of the anterior pituitary to release ACTH (see Figure 2-25).

MNEMONIC

GFR (glomerulosa, fasciculate, reticularis) corresponds with **S**alt (Na^+), **S**ugar (glucocorticoids), and **S**ex (androgens). "The deeper you go, the sweeter it gets."

FLASH FORWARD

21-Hydroxylase deficiency, the most common form of **congenital adrenal hyperplasia** (CAH), leads to decreased levels of both glucocorticoids and mineralocorticoids with a concomitant rise in androgens. Clinically, patients show **hypo**tension, hyponatremia, **hyper**kalemia, and masculinization.

FLASH FORWARD

In **17α-hydroxylase deficiency**, individuals lack the enzyme to synthesize cortisol or androgens, resulting in the accumulation of a shared precursor, pregnenolone (see Figure 2-25). Clinically, individuals are **hyper**tensive and **hypo**kalemic owing to shunting of pregnenolone into the synthetic pathway of aldosterone.

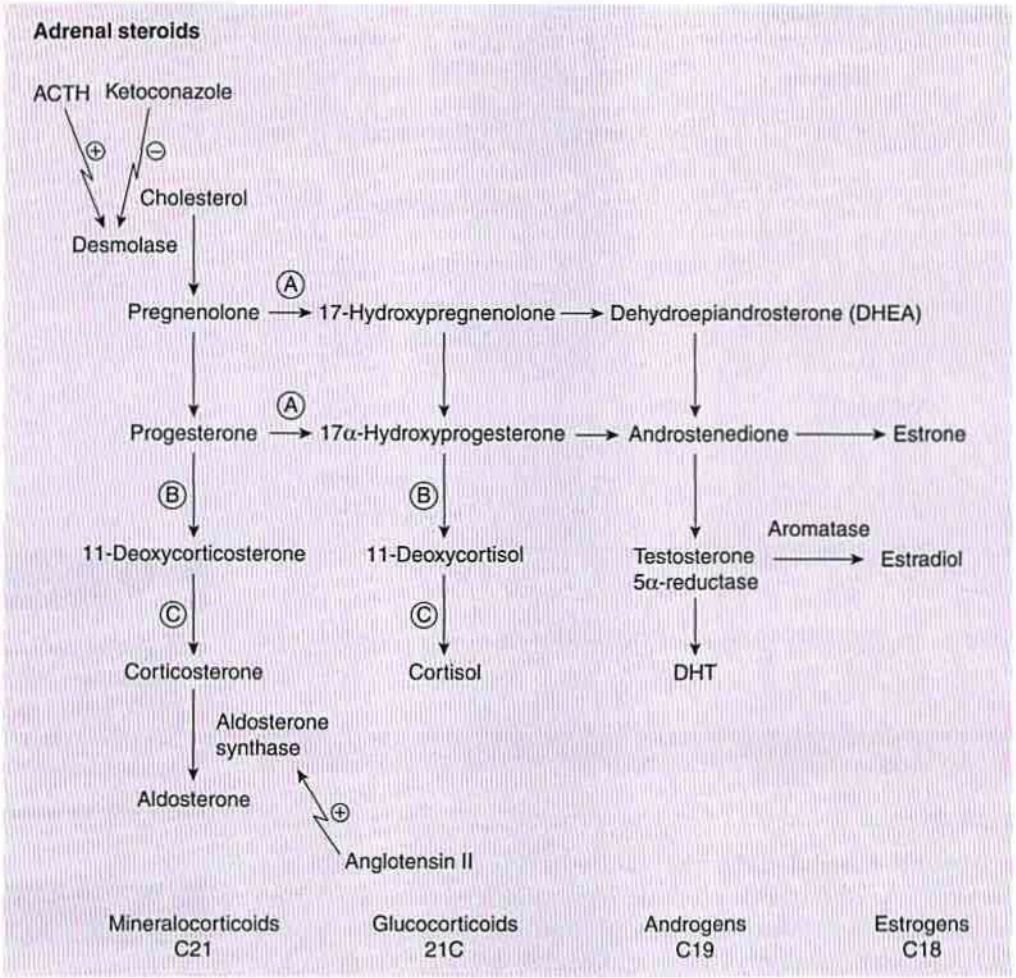


FIGURE 2-24. Steroid hormone synthetic pathways.

- ACTH upregulates desmolase, the rate-limiting step in cholesterol and, in turn, cortisol synthesis. ACTH also promotes gland hypertrophy.
- While CRH and ACTH stimulate cortisol production, the system employs negative feedback to provide regulation. High levels of cortisol inhibit CRH and ACTH secretion (see Figure 2-25).

Glucocorticoids

Glucocorticoids, so named for their effects on blood glucose levels, are now recognized for a diverse set of actions including alterations in immune function, bone turnover, and cardiovascular function.

- **Cortisol:** Predominant glucocorticoid (provides 95% of endogenous glucocorticoid activity); potent (see Table 2-21 for overview of stress hormones).
- **Corticosterone:** Immediate precursor to cortisol (provides < 5% of endogenous glucocorticoid activity); low potency.
- **Cortisone, prednisone, methylprednisolone, and dexamethasone:** Synthetic glucocorticoids with various potencies relative to cortisol (see Table 2-22).

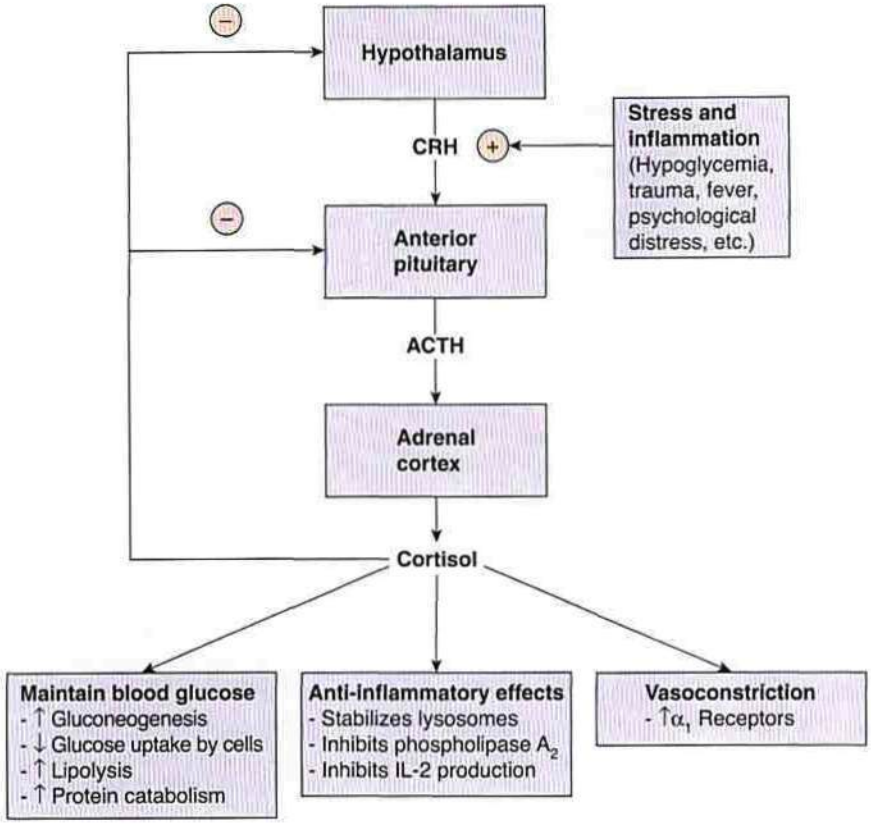


FIGURE 2-25. Effects and regulation of cortisol.

Actions of Cortisol

Cortisol plays multiple roles in maintaining homeostasis, influencing the immune response, intermediary metabolism, vascular tone, and to a limited extent, renal function.

- **Promotes energy mobilization via gluconeogenesis:** Cortisol effectively increases blood glucose concentration. Cortisol reduces the uptake of glucose into cells, while simultaneously increasing the amount of substrate (gluconeogenic amino acids and glycerol) for glucose conversion in the liver. Cortisol does so by stimulating lipolysis and protein catabolism, lead-

TABLE 2-21. Stress Hormones

GH	▪ Increases lipolysis in adipose tissue ▪ Promotes protein synthesis
Glucagon	▪ Increases lipolysis in adipose tissue ▪ Stimulates glycogenolysis ▪ Promotes gluconeogenesis
Cortisol	▪ Increases lipolysis in adipose tissue ▪ Stimulates gluconeogenesis ▪ Upregulates vascular adrenergic (α_1) receptors
Epinephrine	▪ Increases lipolysis in adipose tissue ▪ Promotes glycogenolysis

TABLE 2-22. Synthetic Glucocorticoids

Synthetic Steroid	Potency (Relative to Cortisol)
Cortisone	1 ×
Prednisone	4 ×
Methylprednisolone	5 ×
Dexamethasone	30 ×

ing to the mobilization of fatty acids and amino acids, respectively (see Figure 2-25).

- **Anti-inflammatory effects:** Cortisol both prevents inflammation and reduces existing inflammatory conditions.
  - By stabilizing lysosomal membranes, it reduces the risk of lysosomal membrane rupture and minimizes the amount of proteolytic enzymes acting within the inflammatory milieu.
  - It promotes the synthesis of lipocortin, an inhibitor of phospholipase A_2. Phospholipase A_2 normally supplies arachidonic acid for the synthesis of prostaglandins and leukotrienes. Lack of these local inflammatory mediators decreases capillary permeability and the recruitment of leukocytes to the inflamed tissue.
  - Cortisol decreases production of inflammatory cytokines (e.g., TNF-α) leading to a reduction in macrophage activation.
  - Cortisol also boosts the function of the adaptive immune system by inhibiting the production of interleukin-2 (IL-2), a cytokine involved in promoting T-cell proliferation. Other cytokines are also disrupted in this process.
  - Lastly, cortisol blocks the release of histamine from mast cells and serotonin from platelets, thereby inhibiting allergic reactions.
- **Adrenergic receptor upregulation:** Cortisol helps smooth muscle maintain responsiveness to the vasoconstrictive effects of norepinephrine by upregulating α_1-adrenergic receptors on vascular smooth muscle cells. Cortisol also contributes to vascular tone through inhibition of nitric oxide synthase, decreasing the production of the vasodilator nitric oxide.
- **Mineralocorticoid activity:** Though its mineralocorticoid effects are normally negligible relative to its marked glucocorticoid activity (because it is inactivated by renal 11-hydroxysteroid dehydrogenase), in disease states characterized by very high concentrations, cortisol can exert a potent mineralocorticoid effect.

KEY FACT

Cortisol promotes gluconeogenesis and suppresses inflammation under conditions of stress.

FLASH FORWARD

Synthetic glucocorticoids (e.g., prednisone) are commonly used in the acute management of inflammatory conditions such as asthma and rheumatoid arthritis.

FLASH FORWARD

Cushing's syndrome is characterized by increased cortisol levels, producing the classic clinical picture: Hypertension, central obesity, weight gain, moon facies, insulin resistance, skin thinning/striae, buffalo hump, osteoporosis, and amenorrhea (see Table 2-23 for overview of abnormal cortisol states).

MINERALOCORTICOIDS

Mineralocorticoid Synthesis and Regulation

ACTH promotes aldosterone secretion (see Figure 2-24 for its synthetic pathway); however, it has little to no effect on the **rate of secretion**. Only modest quantities of ACTH are necessary to initiate aldosterone synthesis. The rate of secretion is then either increased or decreased from the basal level, depending on changes in the ECF volume, sodium or potassium concentrations in the ECF, and arterial pressures. The most important determinants of aldosterone secretion are:

TABLE 2-23. Abnormal Cortisol States

Disorder	Cortisol	ACTH
Primary hypercortisolism (Cushing's syndrome)	↑	↓
Secondary hypercortisolism (Cushing's disease)	↑	↑
Primary adrenal insufficiency (Addison's disease)	↑	↑
Secondary adrenal insufficiency	↑	↑

- **High serum potassium** increases secretion.
- The **RAS** increases secretion.
- **High serum sodium** decreases secretion (minimally).

Actions of Aldosterone

Aldosterone has three major and related effects: Increased sodium reabsorption, increased BP, and increased potassium excretion.

- **Increased sodium reabsorption:** Aldosterone stimulates the synthesis of new sodium channels in the principal cells of the collecting tubules. These additional sodium channels promote sodium reabsorption and reduce sodium excretion in the urine.
- **Increased arterial pressure:** Aldosterone increases total sodium reabsorption, but does not significantly alter serum sodium concentration. This is because water is also reabsorbed by the collecting tubules. The net effect is an increase in extracellular volume, which, over time, can cause arterial pressure to rise.
- **Increased potassium secretion:** Aldosterone induces the opening of large numbers of sodium and potassium channels in the principal cells of the collecting ducts. Enhanced sodium reabsorption is accompanied by increased potassium secretion into the tubule lumen.

KEY FACT

Activation of the RAS and high serum potassium are the major stimulus for the release of aldosterone from the adrenal cortex.

FLASH FORWARD

In **Conn's syndrome**, or primary aldosteronism, excessive aldosterone is produced by adrenocortical adenomas, carcinomas, or hyperplasia of the zona glomerulosa. Patients are generally **hypertensive** and **hypokalemic.**

ADRENAL ANDROGENS

Adrenal androgens (androstenedione, DHEA, and dehydroepiandrosterone sulfate [DHEA-S]) play a relatively minor role in homeostasis, in part because these steroid hormones are relatively weak androgens and make up a small percentage of circulating sex steroids. Nonetheless, there are several periods during development when adrenal androgens take on a more important role.

- **Fetal development:** During pregnancy, because the placenta cannot synthesize cholesterol from acetate, it is incapable of producing sex steroids de novo. Instead, it produces androgens and estrogens from precursors (e.g., DHEA-S) produced by the maternal and fetal adrenal glands.
- **Adrenarche:** Adrenarche is a stage of adrenal maturation marked by increased synthesis of androgens resulting in pubic and axillary hair growth during puberty. The weak androgens released from the adrenals are peripherally converted to the more powerful androgens testosterone and dihydrotestosterone (DHT), which ultimately act in secondary sexual differentiation in both sexes.
- **Menopause:** Menopause is marked by a cessation of ovarian estrogen production; however, postmenopausal women are not completely estrogen deficient. Androstenedione produced by the adrenals and ovaries is peripherally converted to estrone by the enzyme **aromatase.** Estrone is a weaker estrogen relative to estradiol, the major premenopausal estrogen;

FLASH FORWARD

Estrogen potency: Estradiol > estrone > estriol

FLASH FORWARD

Because patients with **11β-hydroxylase deficiency** lack an enzyme in the adrenal steroid synthetic pathway (see Figure 2-24), they cannot produce normal levels of cortisol and aldosterone. The steroid precursors are shunted into the production of excessive quantities of sex hormones. Consequently, patients with 11β-hydroxylase deficiency are **hypertensive** and females are **virilized**.

consequently, estrone does not provide adequate protection against the long-term consequences of estrogen deficiency (e.g., osteoporosis, vasomotor symptoms, and cardiovascular changes).

DISORDERS OF THE ADRENAL GLAND

Cushing's Syndrome

Cushing's syndrome refers to excess cortisol, and is most commonly caused by iatrogenic overadministration. Other causes include pituitary adenomas (excess ACTH from the pituitary → bilateral adrenal hyperplasia), adrenal tumors, and ectopic ACTH production (small cell carcinoma of the lung, bronchial carcinoid tumors).

PRESENTATION

Patients with Cushing's syndrome present with features consistent with excess cortisol (see Figure 2-26).

- Central obesity, moon facies, buffalo hump
- Hypertension
- Glucose intolerance (decreased peripheral glucose utilization, increased hepatic gluconeogenesis)
- Purple striae
- Muscle wasting and weakness
- Osteoporosis
- Depression and mania
- Decreased immunity → increased risk of infections

DIAGNOSIS

Initial screen is the overnight dexamethasone (a cortisol analog) suppression test (see Figure 2-27). In normal individuals, it suppresses ACTH release from the pituitary and results in decreased cortisol release. In Cushing's syndrome, cortisol levels will fail to be suppressed and remain high. A 24-hour urinary free cortisol excretion can be use to confirm the diagnosis. If the urine test is still abnormal, a high-dose dexamethasone suppression test is used. Cortisol

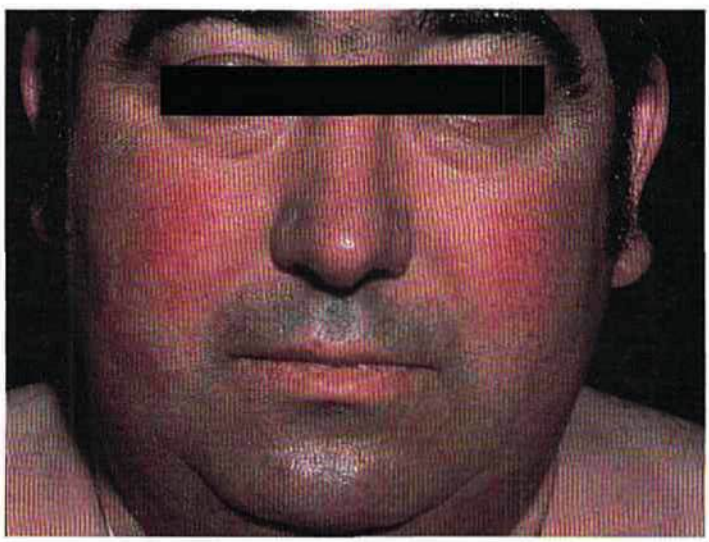


FIGURE 2-26. Presentation of Cushing's syndrome. (Reproduced, with permission, from Wolff K, Johnson RA, Suurmond, D, *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed, New York: McGraw-Hill, 2005: 442.)

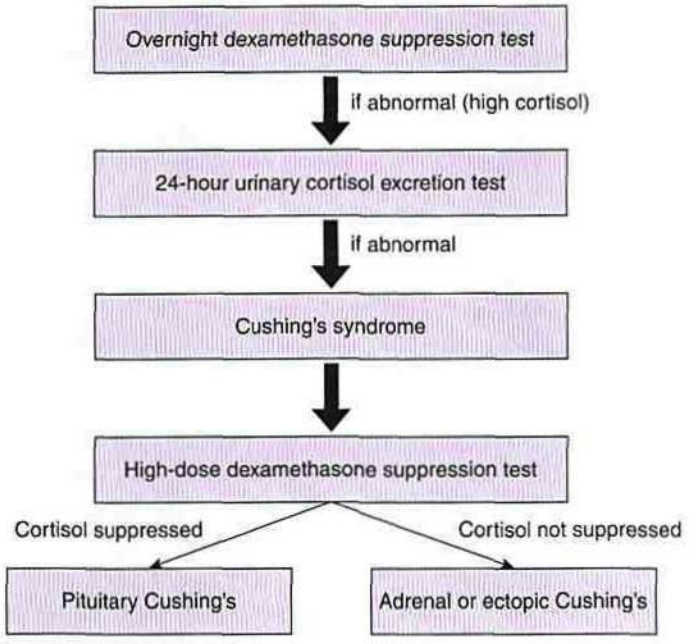


FIGURE 2-27. Diagnosis of Cushing's syndrome.

will be suppressed in pituitary Cushing's, but not in ectopic Cushing's (see Table 2-24).

Primary Hyperaldosteronism (Conn's Syndrome)

Conn's syndrome is caused by excess secretion of aldosterone, causing increased sodium retention and potassium secretion. Primary aldosteronism is most commonly due to a benign adenoma in the zona glomerulosa. Secondary causes include:

- Renin-secreting tumors, renovascular disease such as renal artery stenosis, and malignant hypertension.
- Edematous state with decreased arterial volume (CHF, cirrhosis, nephrotic syndrome), and hypovolemia, diuretics, and genetic diseases like Bartter's syndrome (defective Na-K-Cl transporter), or Gitelman's syndrome (defective Na-Cl transporter).
- Excess non-aldosterone mineralocorticoid due to exogenous mineralocorticoids, CAH, and licorice (leads to build-up of precursors of cortisol).

TABLE 2-24. Summary of Cushing's Syndrome

	Serum/Urine Cortisol	ACTH	High-Dose Dexamethasone Test
Pituitary Cushing's	↑	↑	Cortisol suppressed
Adrenal Cushing's	↑	↓	Cortisol not suppressed
Ectopic Cushing's	↑	↓	Cortisol not suppressed

Presentation

- Sodium and water retention causes hypertension. Hypokalemia causes symptoms of muscle weakness and polydipsia/polyuria.
- Excess aldosterone causes increased Na reabsorption and increased K and H^+ secretion → hypernatremia, hypokalemia, and metabolic alkalosis.

Diagnosis

Screen for hypertension.

- **Labs:** Na, decreased K, and H^+.
- **Hormones:** Both aldosterone and renin are measured. Because of the high aldosterone levels, renin is suppressed. A low renin-aldosterone level (< 0.05) is diagnostic.
- **Sodium suppression test:** Sodium load patient and then measure for appropriate aldosterone suppression. Infusion of saline normally decreases aldosterone levels, but will not do so in Conn's syndrome.

Treatment

Surgery to remove the adenoma in the adrenal gland. Spironolactone inhibits aldosterone action on the kidneys. Other antihypertensives can also be used.

Addison's Disease

Addison's disease is most commonly due to autoimmune destruction of the adrenal glands. Primary causes include infection (TB, cytomegalovirus, histoplasmosis, disseminated meningococcemia in **Waterhouse-Friderichsen syndrome**), vascular disorders (hemorrhage or infarction), metastasis, infiltrative disease (hemochromatosis, amyloid, sarcoidosis), and drugs such as ketoconazole and rifampin. Secondary causes most commonly include abrupt **withdrawal of corticosteroids, or any cause of primary or secondary panhypopituitarism leading to decreased ACTH secretion**.

Presentation

Most commonly presents with weakness, fatigue, anorexia, nausea/vomiting, orthostasis, hyponatremia, and hypoglycemia, which stem from decreased cortisol.

- Increased ACTH in primary adrenal insufficiency leads to skin **hyperpigmentation** (due to MSH in ACTH), hyperkalemia; decreased aldosterone leads to hypotension (due to salt loss), weakness, and hypoperfusion leading to syncope.

Diagnosis

- **ACTH challenge:** Administer ACTH to boost cortisol. Normally, the adrenal gland increases its production of cortisol in response to ACTH. In primary and chronic secondary adrenal insufficiency, there is no increase in cortisol production when ACTH is given. In acute secondary adrenal insufficiency, cortisol may be normal.
- **Labs:** Decreased Na, increased K, decreased glucose.
- **Endocrine:** Decreased cortisol levels; ACTH may be elevated (primary), or decreased (secondary).
- **CBC:** Increased eosinophil count.

Treatment

Treatment for Addison's disease involves replacement of glucocorticoids and mineralocorticoids.

Congenital Adrenal Hyperplasia

CAH is a group of autosomal recessive disorders that cause cortisol deficiency, which results in increased corticotropin production and adrenal gland hyperplasia.

Treatment

Glucocorticoids prevent excess ACTH secretion from stimulating the adrenal gland.

Pheochromocytoma

Pheochromocytoma arises from the chromaffin cells, which are mainly located in the adrenal medulla (10% are extra-adrenal). Pheochromocytoma may be associated with MEN types IIA and IIB, neurofibromatosis, and von Hippel-Lindau syndrome.

Presentation

Hypertension, palpitations, anxiety, weight loss.

Diagnosis

- 24-hour urinary metanephrine and vanillylmandelic acid (breakdown products of catecholamines).
- Clonidine suppression test → clonidine normally decreases NE, but it remains elevated in patients with pheochromocytoma.

Treatment

The treatment of choice is surgical removal of the pheochromocytoma. Medical therapy involves use of α-blockers (phenoxybenzamine, phentolamine) and β-blockers.

KEY FACT

Hypertension: 17α-Hydroxylase deficiency
Increased sex hormones: 21-Hydroxylase deficiency
Increased sex hormones and hypertension: 11β-Hydroxylase deficiency

KEY FACT

MEN syndrome

- MEN 1 (Wermer's syndrome) = three Ps (**P**arathyroid hyperplasia, **P**ancreatic islet cell tumors, **P**ituitary tumors)
- MEN type 2A (Sipple's syndrome) = "**MPH**" (**M**edullary thyroid carcinoma, **P**heochromocytoma, **H**yperparathyroidism)
- MEN type 2B = "**MMP**" (**M**edullary thyroid carcinoma, **M**ucosal neuromas, **P**heochromocytomas)

KEY FACT

Pheochromocytoma rule of 10s:
10% Familial
10% Bilateral
10% Malignant
10% In children
10% Extra-adrenal

Pancreas

The pancreas is a multifunctional organ of the endocrine and digestive systems. The endocrine pancreas plays a vital role in carbohydrate, lipid, and protein metabolism through the secretion of two hormones: insulin and glucagon.

ANATOMY

The pancreas is a retroperitoneal organ situated posterior to the stomach. It lies between the duodenum and spleen (see Figure 2-28). It is divided into four segments: Head, neck, body, and tail. The pancreatic head lies adjacent to the second segment of the duodenum, while the tail abuts the spleen. The body of the pancreas lies transversely across the retroperitoneum. (**The pancreatic ductal system is discussed in the gastrointestinal chapter.**)

The **arterial blood supply** to the pancreas is composed of:

- **Pancreatic arteries:** Supply the body and tail of the pancreas, and are derived from splenic artery.
- **Superior pancreaticoduodenal:** Supplies the head of the pancreas, and is derived from the gastroduodenal artery.
- **Inferior pancreaticoduodenal:** Supplies the head of the pancreas, and is derived from the SMA.

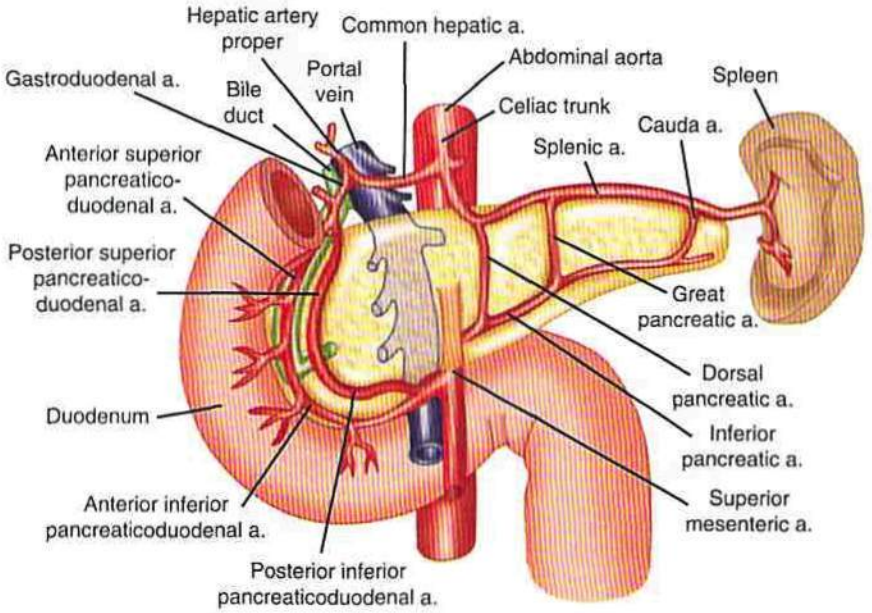


FIGURE 2-28. Anatomy of the pancreas with its arterial supply.

FLASH FORWARD

Because of its transverse orientation anterior to the vertebral column, the pancreas is susceptible to rupture following severe abdominal trauma (e.g., automobile accidents). Seat belts transmit large compressive forces on the abdomen that effectively drive the vertebral column through the body of the pancreas.

The **venous drainage** of the pancreas is provided by **pancreatic veins** that drain into the portal vein from tributaries of the splenic vein and superior mesenteric vein.

FLASH FORWARD

An **annular pancreas** develops when impaired rotation of the pancreatic buds prevents normal fusion. The buds remain wrapped around the duodenum, which is manifest as polyhydramnios and duodenal obstruction.

EMBRYOLOGY

The primitive gut tube is composed of the foregut, midgut, and hindgut. Foregut derivatives include the esophagus, stomach, upper duodenum, liver, gallbladder, and pancreas.

The mature pancreas develops from two separate buds of tissue off the foregut: The ventral and dorsal pancreatic buds. The ventral bud gives rise to the pancreatic head and uncinate process, while the dorsal bud forms the remaining components of the pancreas.

During development, the buds rotate and fuse to form a complete pancreas derived primarily from endoderm (acinar cells, islet cells, and acinar epithelium are endoderm derivatives).

Pancreatic exocrine and endocrine functions begin at different stages of development. Exocrine function begins shortly after birth, whereas endocrine signaling commences at weeks 10–15 of development. The developing fetus can begin to regulate blood glucose levels relatively early in development.

FLASH FORWARD

During pregnancy, a woman with diabetes must strictly control her blood glucose levels. Maternal glucose crosses the placenta during pregnancy and causes fetal hyperinsulinemia. Hyperglycemia has adverse effects on the developing fetus, increasing the risk of fetal congenital anomalies. Following delivery, rapid withdrawal of high glucose levels in the setting of persistent hyperinsulinemia in the neonate may result in severe hypoglycemia.

HISTOLOGY

The islets of Langerhans are clusters of hormone-producing cells interspersed within pancreatic exocrine tissue. Each islet contains hundreds of endocrine cells surrounded by rich capillary networks. Approximately 1 million islets are found across the pancreas, with greater numbers located in the tail.

TABLE 2-25. Islet Cell Types and Function

Cell Type	Quantity	Location	Hormone	Function
Alpha (α)	20%	Periphery	Glucagon	Increases blood glucose
Beta (β)	70%	Central	Insulin	Decreases blood glucose
Delta (δ)	< 5%	Variable	Somatostatin	Inhibits release of other islet cell hormones
F-type	Rare	Variable	Pancreatic polypeptide	Control of gastric secretion? Control of islet secretion?

(Adapted, with permission, from Junqueira LC, Carneiro J, *Basic Histology: Text & Atlas*, 11th ed, New York: McGraw-Hill, 2005: 408.)

The three major cell populations within islets are shown in Table 2-25.

Autonomic nerve fibers innervate the blood vessels and endocrine cells of the pancreatic islets. The sympathetic and parasympathetic nervous systems influence insulin and glucagon secretion. Because nerve fibers are in close apposition with only 10% of islet endocrine cells, gap junctions play a role in the spread of signals to the remaining cells.

FLASH FORWARD

In **type 1 DM (DM-1)**, autoimmune destruction of pancreatic β cells leads to insulin insufficiency.

INSULIN

Biosynthesis

Insulin is a small protein composed of two polypeptide chains, A and B, joined by disulfide linkages. It is synthesized as a preprohormone. A series of proteolytic reactions in the endoplasmic reticulum and Golgi complex generate the biologically active form of insulin (51 amino acids) and an inactive peptide referred to as **C-peptide** (31 amino acids). C-peptide is derived from the cleavage of proinsulin to form insulin. Upon stimulation of the β cell, insulin and C-peptide are released into the circulation in equimolar quantities.

FLASH FORWARD

In patients with hypoglycemia secondary to high circulating insulin levels, C-peptide levels help distinguish between endogenous (e.g., insulinoma) and exogenous (e.g., surreptitious use) sources.

Secretion

Glucose is the most powerful stimulus for insulin release (see Table 2-26). Glucose enters β cells via the glucose transporter **GLUT 2**. This transport is by facilitated diffusion, meaning that the intracellular glucose concentration

TABLE 2-26. Factors Affecting Insulin Release

Promote Insulin Secretion	Inhibit Insulin Secretion
Glucose	α-Adrenergic stimulation
Amino acids	Somatostatin
Vagal stimulation	Drugs: Phenytoin, vinblastine, colchicine
Sulfonylureas	
CCK, GIP, glucagon-like peptide	
Secretin, gastrin	
β-Adrenergic stimulation	

equilibrates with the serum glucose concentration. Increases in serum glucose within β cells are shunted into the glycolytic pathway. Increased glucose catabolism leads to a rise in the intracellular ATP:ADP ratio, which causes the **ATP-sensitive potassium channel** on the surface of β cells to close. Closure of this potassium channel leads to depolarization of the cell resulting in opening of calcium channels. This rise in intracellular calcium facilitates insulin release from the cell (see Figure 2-29).

Another mediator of insulin release is the second messenger cAMP. Serum glucose stimulates cAMP formation within the β cell, which mobilizes intracellular calcium stores. This calcium combines with calcium entering as a result of membrane depolarization (see above) to increase insulin secretion.

Insulin Receptor Activation

Stimulation of the insulin receptor leads to downstream signaling cascades that result in alterations in metabolism and growth.

- The insulin receptor is a member of the GF family. It consists of two entirely extracellular α subunits and two transmembrane β subunits linked by disulfide bonds. The β subunits have tyrosine kinase activity.
- Insulin binds to the α subunits of its receptor, resulting in autophosphorylation and activation of the β subunits. The activated β subunits recruit additional proteins to the cell membrane, including adapter molecules, kinases, and phosphatases (see Figure 2-30).
- Two signaling pathways exist downstream of the activated insulin receptor:
  - **Mitogenic pathway:** Responsible for the growth-promoting effects of insulin due to activation of the MAP kinase cascade

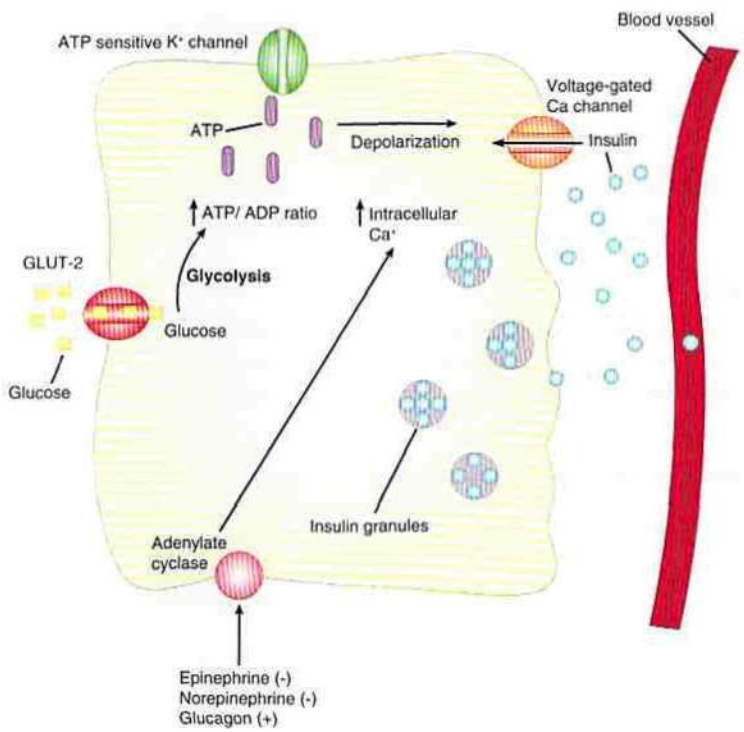


FIGURE 2-29. Pancreatic β cell insulin secretion.

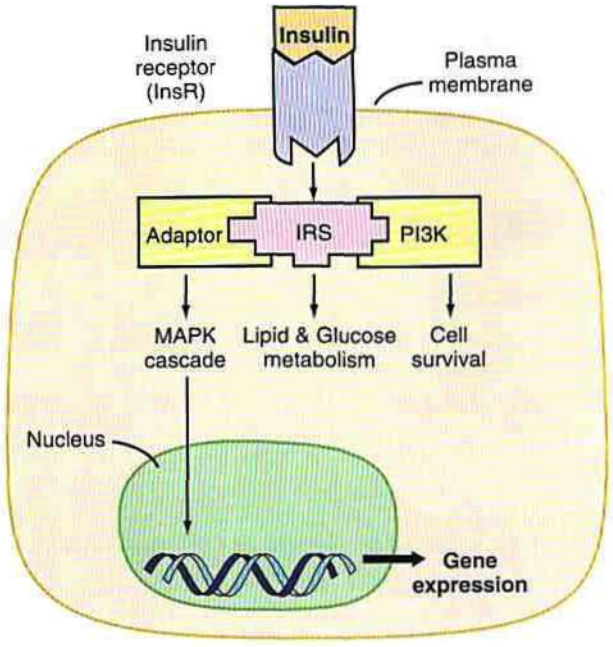


FIGURE 2-30. Insulin receptor and downstream signaling. (Modified, with permission, from Brunicardi FC, *Schwartz's Principles of Surgery*, 8th ed, New York: McGraw-Hill, 2005: 412.)

- **Metabolic pathway:** responsible for alterations in nutrient metabolism
  - Activation of phosphatidylinositol-3-kinase in the metabolic pathway leads to GLUT-4 transporter insertion in the cellular membrane and stimulation of anabolic pathways
- Insulin-bound receptors are internalized within the cell membrane following continued exposure to insulin. This downregulation desensitizes target tissues to the effects of insulin.
- In response to low insulin levels, target tissues upregulate the number of insulin receptors on their surfaces.

Action

Insulin's actions on carbohydrate and lipid metabolism are mediated mainly by three types of tissues: Liver, muscle, and fat. The coordinated actions of insulin at these tissues promote the storage of nutrients by the body.

- Effects on the liver:
  - Stimulates glycogen formation (upregulates activity of glucokinase and glycogen synthase).
  - Inhibits glycogenolysis (glycogen phosphorylase activity reduced).
  - Inhibits gluconeogenesis (phosphofructokinase activity enhanced).
  - Inhibits catabolism of fatty acids and amino acids.
  - Promotes triglyceride synthesis.
- Effects on muscle:
  - Increases glucose uptake (promotes insertion of GLUT 4 on target cell membranes).
  - Stimulates glycogen formation (upregulates activity of glycogen synthase).
  - Increased amino acid uptake and protein synthesis.
  - Decreased protein degradation.

- Effects on fat:
  - Increased glucose uptake (promotes insertion of GLUT 4 on target cells).
  - Increased triglyceride storage (enhanced lipoprotein lipase activity promotes triglyceride hydrolysis from lipoproteins).

GLUCAGON

Biosynthesis and Secretion

Glucagon is a counterregulatory polypeptide secreted by pancreatic α cells. The stimuli for glucagon secretion include amino acids, catecholamines, gastric hormones, glucocorticoids, and most importantly, hypoglycemia (see Table 2-27).

ACTION

The main action of glucagon is to promote elevations in blood glucose concentrations. Glucagon is a catabolic hormone that balances the energy-storing (anabolic) effects of insulin. The major site of action of glucagon is the liver. It stimulates surface-bound receptors on hepatocytes, thereby activating AC and raising the levels of cAMP within cells. cAMP is the second messenger responsible for mediating the downstream effects of glucagon. The major actions of glucagon are:

- **Promotes increases in serum glucose:**
  - Increased glycogenolysis (secondary to increased glycogen phosphorylase activity).
  - Increased gluconeogenesis (secondary to decreased phosphofructokinase activity).
  - Increased amino acid uptake by liver (provides substrate for gluconeogenesis).
- **Stimulates increases in serum fatty acids:**
  - Activates adipose cell lipase, thereby increases serum free fatty acids.
  - Inhibits storage of triglycerides in the liver.
- **Leads to elevations in urea production:**
  - Amino groups from catabolized amino acids are shunted into the urea cycle.

The minor actions of glucagons are:

- Increased bile secretion.
- Increased cardiac contractility.
- Decreased gastric acid secretion.
- Increased local blood flow in selected tissues.

TABLE 2-27. Factors Affecting Glucagon Secretion

↑ GLUCAGON SECRETION	↓ GLUCAGON SECRETION
Hypoglycemia	Hyperglycemia
Norepinephrine, epinephrine	Fatty acids
Amino acids	Somatostatin
CCK, gastrin	Insulin
Glucocorticoids	

SOMATOSTATIN

Somatostatin is a relatively small polypeptide (14 amino acids) secreted by the pancreatic δ cells in response to high levels of blood glucose, amino acids, fatty acids, and gastric hormones. Somatostatin lengthens the period over which nutrients are incorporated into the circulation. Actions of somatostatin include:

- Decreased secretion of insulin and glucagon (paracrine effect).
- Decreased gastric, duodenal, and gallbladder motility.
- Decreased function of intestinal mucosa (decreased absorption and secretion).

DISORDERS OF THE ENDOCRINE PANCREAS

Diabetes Mellitus

Hyperglycemia is the key feature in DM, which results either from reduced insulin secretion (type 1, DM-1) or tissue resistance to insulin (type 2, DM-2) (see Table 2-28). Complications of DM can be divided into neuropathy, microvascular disease (retinopathy, nephropathy), and macrovascular disease (atherosclerosis).

PRESENTATION

- Polyuria, polydipsia (glucose-induced osmotic diuresis → dehydration).
- Macrovascular complications:
  - Atherosclerosis: Advanced glycosylation end-products (AGE) produce changes in collagen composition in arterial walls and traps LDL, leading to increased lipid deposition.
  - Coronary artery disease.
  - Peripheral vascular disease.
  - Strokes.
- Microvascular complications:
  - Diabetic nephropathy: Hyalinization of glomerular arterioles (**Kimmelstiel-Wilson syndrome**), proteinuria/microalbuminuria.
  - Diabetic retinopathy (see Figure 2-31).

TABLE 2-28. DM-1 and DM-2

FEATURE	DM-1	DM-2
Percentage of DM cases	10%	90%
Prevalence	0.2%–0.5%	2%–4%
Age of onset	< 30	> 40
Pathogenesis	Family history uncommon; HLA-B8, -B15, -DR3, and -DR4 association; autoimmune islet β-cell destruction	Family history common (90%–100% concordance rate for identical twins)
Body habitus	Thin	Obese (fat reduces number of insulin receptors)
Treatment	Insulin	Diet; oral hypoglycemic drugs; insulin
Dreaded complications	Ketoacidosis prone	Hyperosmolar nonketotic coma

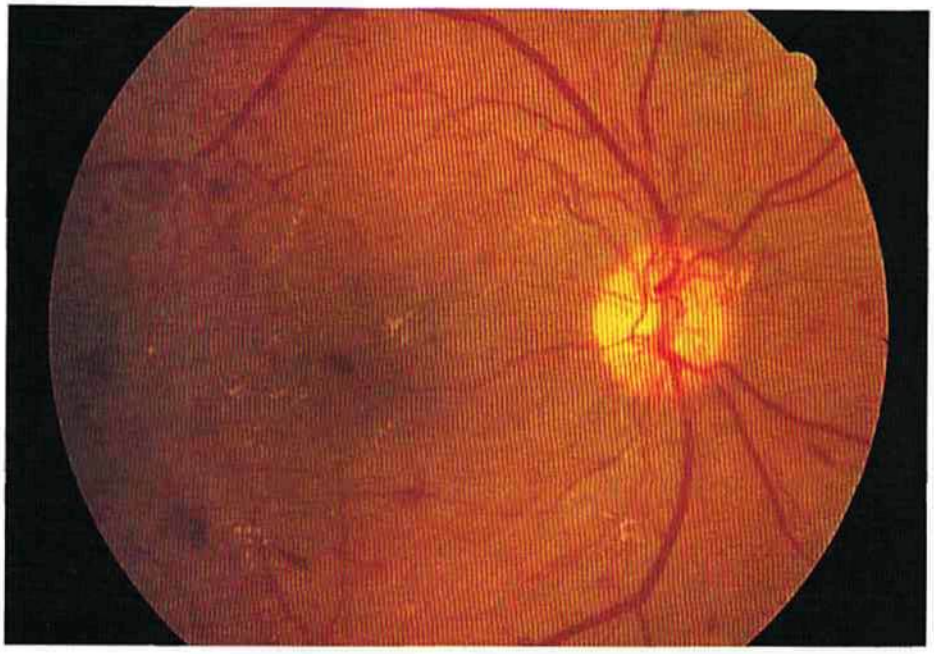


FIGURE 2-31. Diabetic retinopathy showing exudates, microaneurysms, and blot hemorrhages. (Reproduced, with permission, from Kasper DL, Braunwald E, Fauci AS, et al, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 2163.)

- Diabetic neuropathy: Peripheral neuropathy (loss of pain and vibratory sensation), autonomic neuropathy (sexual impotence, delayed gastric emptying).

Pathogenesis of Diabetic Ketoacidosis (DKA)

DKA is a complication of DM-1. Events (e.g., forgetting to take insulin, infections, illnesses, excess alcohol ingestion) that decrease insulin precipitate ketoacidois. Lack of insulin causes lipolysis and releases free fatty acids from adipose tissues. Patients present with:

- Kussmaul's respirations (rapid, deep breathing)
- Acetone in breath (fruity odor)
- Dehydration, orthostatic hypotension
- Altered consciousness/coma

Decreased insulin → increased lipolysis → increased glycerol and free fatty acids → β-oxidation of free fatty acids → increased ketones.

Diagnosis (See Table 2-29)

- Glycosylated HbA_{1c} provides a way to monitor glucose control over the preceding 2–3 months. Ideal goal is to keep $HbA_{1c} < 7\%$ (see Table 2-30).

TABLE 2-29. Diagnostic Criteria for Diabetes

Test	Diabetes Criteria
Random plasma glucose	> 200 mg/dL with symptoms
Fasting glucose	> 125 mg/dL on two occasions

TABLE 2-30. Interpretation of HbA_{1c} Levels

> 10%	Poor control
8.5%–10%	Fair control
7%–8.5%	Good control
< 7%	Ideal control

Treatment

Insulin is usually given by SC injection; it can also be given IV for emergency situations (DKA). All DM-1 patients need insulin. For DM-2 diabetics, diet and exercise should be the first line of therapy. Most require pharmacologic treatment, including oral hypoglycemic drugs (metformin, sulfonylurea) and some also need insulin. Complications include fungal infections, particularly *Candida albicans*, and nonhealing ulcers and wounds.

Insulinoma

An uncommon cause of hypoglycemia in non-diabetics, insulinomas result from tumors of β cells in the pancreas. Often associated with MEN 1 syndrome. Other causes of hypoglycemia that must be ruled out include exogenous insulin or sulfonylureas, anti-insulin antibodies, or decreased glucose production secondary to adrenal insufficiency, liver failure, alcoholism, hypopituitarism, glucagon deficiency, and sepsis.

Presentation

Patients with insulinomas present with Whipple's triad:

- Fasting hypoglycemia.
- Symptoms of hypoglycemia (excessive epinephrine → sweating, tremor, tachycardia; CNS dysfunction → dizziness, headache, change in mental status).
- Relief of symptoms after IV glucose.

Diagnosis

Increased insulin + C-peptide.

- Chemistries: Check glucose level and C-peptide; if increased insulin but decreased C-peptide, then it is factitious hypoglycemia (see Table 2-31).
- β-OH butyrate.
- BUN/Cr, LFTs, TFTs.
- IGF-1.

KEY FACT

Causes of hypoglycemia:

- Exogenous insulin
- Insulinomas
- Ethanol ingestion
- Postoperative complication of gastric surgery
- Reactive hypoglycemia
- Liver failure

TABLE 2-31. Insulinoma vs. Factitious Hypoglycemia

	Insulinoma	Factitious hypoglycemia
Serum insulin	↑	↑
C-peptide	↑	↓

TABLE 2-32. Other Tumors of the Pancreatic Islet Cells

TUMOR	FEATURES	DIAGNOSIS
Gastrinoma (Zollinger-Ellison syndrome)	Excess gastrin release leads to ↑ acid and peptic ulcer disease.	▪ ↑ Basal acid output (BAO) ▪ IV secretin test shows ↑ gastrin.
Glucagonoma	▪ Tumor of α cells. ▪ Associated with diabetes. ▪ **Necrolytic migratory erythema** (red, scaly rash).	Glucagon levels not suppressed by glucose.
VIPoma (Verner-Morrison syndrome, pancreatic cholera)	Increase in vasoactive intestinal peptide (VIP); watery diarrhea; hypokalemia; achlorhydria.	**Clinical.**

TREATMENT

Surgical resection is used to treat insulinomas. For acute treatment for other causes of hypoglycemia, sugar-containing foods are given by mouth. If the patient cannot eat, D50W is given.

Methods of treatment of other types of tumors of the islet cells are shown in Table 2-32.

DIABETES DRUGS

Those with DM-1 require insulin, while those with DM-2 can be managed by lifestyle modifications (exercise, diet), oral hypoglycemic drugs, and/or insulin. The goals of diabetic pharmacologic therapy are to control acute symptoms and limit future complications.

Insulin

Insulin is self-administered by subcutaneous injection, typically in the abdomen, arms, or legs. It can be given IV in emergency situations (i.e., DKA). It is usually given as two-thirds of the daily dose in the morning and one-third of the daily dose in the evening. There are new inhaled forms as well.

MECHANISM

Supplies insulin in insulin deficiency (DM-1) or resistance (DM-2), leading to decreased plasma glucose.

USES

DM-1, DM-2, DKA.

- Insulin comes in short-, intermediate-, and long-acting forms that affect its dosing schedule (see Table 2-33).

SIDE EFFECTS

Hypoglycemia.

TABLE 2-33. Types of Insulin

Insulin Type	Onset of Action	Duration of Action	Notes
Ultra-short acting • Insulin lispro • Insulin aspart	20 min	4 h	
Rapid acting • Regular	1 h	6–8 h	Only type of insulin given IV.
Intermediate acting • NPH • Lente	2–4 h	10–18 h	Most widely used type of insulin.
Long-acting • Glargine • Protamine zinc • Ultralente	• 12 h • 14–24 h • 18–24 h	• 24 h • 36 h • 36 h	

ORAL HYPOGLYCEMIC DRUGS

Sulfonylureas

Mechanism

Inhibits potassium channels on β cells, and prevents hyperpolarization and leads to membrane depolarization, increased calcium influx, and insulin release; increased insulin leads to decreased glucagon release from α cells, and increased tissue sensitivity to insulin.

Uses

DM-2; for glucose control after failure of conservative diet and exercise regimen. Successful therapy requires ~ 30% of β-cell function (secondary failure of drug due to decreased β-cell function). Used in thin patients.

- First-generation: Tolbutamide (good in renal dysfunction), chlorpropamide (long acting, may cause SIADH and disulfiram-like reactions).
- Second-generation: Glipizide, glyburide.

Side Effects

Hypoglycemia, weight gain, hypersensitivity; hyperglycemia with cimetidine, insulin, salicylates, sulfonamides.

Metformin

Mechanism

Decrease hepatic glucose production; increase peripheral insulin sensitivity. Exact mechanism of action unknown. Decreases postprandial glucose levels but does not cause weight gain or hypoglycemia (euglycemic).

Uses

First line for obese diabetic patients; synergistic with sulfonylureas, in patients without renal failure. Contraindicated in patients with renal impairment (drug excreted by kidneys).

Side Effects

Lactic acidosis, GI distress (nausea, diarrhea).

Acarbose

Mechanism

Inhibits α-glycosidase → decreased carbohydrate absorption from the GI tract → decreased insulin demand.

Uses

Refractory DM-2.

Side Effects

Flatulence, diarrhea, abdominal discomfort.

Thiazolidinediones (Rosiglitazone, Pioglitazone)

Mechanism

Binds nuclear peroxisome proliferator-activated receptor (PPAR) to control transcription of insulin-responsive genes, leads to insulin sensitization and decreased hepatic gluconeogenesis and insulin receptor upregulation.

Uses

DM-2, in the absence of liver disease.

Side Effects

Weight gain, edema, liver function abnormalities.

Repaglinide

Mechanism

Works like sulfonylureas by stimulating release of insulin from the pancreas.

Uses

DM-2.

Side Effects

Hypoglycemia, weight gain.

Rapid Review

Key Terms

Suprarenal gland	Another name for the adrenal gland.
Cushingoid	Displaying the signs and symptoms of Cushing's disease.
"Hot" nodule	Thyroid nodule that takes up iodine on thyroid scan (thus is functional).
"Cold" nodule	Thyroid nodule that does not take up iodine on thyroid scan (thus is nonfunctional).
Sestamibi scan	Radiologic study using labeled radioactive technetium-99 that is used to locate parathyroid glands prior to surgery.
Hemoglobin A_{1c}	Test used to monitor glycemic control over a period of about 3 months. The higher the level of hyperglycemia, the more elevated the level of glycosylated hemoglobin.
Bitemporal hemianopsia	Classic symptom of pituitary tumors, which due to their location impinge on the optic chiasm, resulting in double or blurry vision.

SUMMARY OF ADRENAL-RELATED HORMONES

See Table 2-34.

Cushing's Syndrome

Syndrome caused by increased cortisol. Presents with a variety of signs and symptoms, including hypertension, weight gain, truncal obesity, "buffalo hump," moon facies, hyperglycemia (secondary to insulin resistance), purple striae (may appear like stretch marks), thinning skin, osteoporosis, amenorrhea, and immunosuppression. Causes can be separated into four broad categories:

- **Exogenous steroids.** Most common cause, from chronic prescription steroid use.
- **Cushing's disease:** Occurs with a primary pituitary adenoma, which produces increased ACTH. Note that Cushing's **disease** is very specific for a pituitary adenoma, while Cushing's **syndrome** has several causes and describes any state that results in increased cortisol production.
- **Adrenal causes:** Functional adenomas may produce increased levels of cortisol. Some adrenal cancers may do so as well.
- **Ectopic ACTH production not by the adrenals:** Occurs in certain paraneoplastic syndromes (i.e., small cell lung cancer).

Hyperaldosteronism

Increased levels of aldosterone resulting from abnormalities within the adrenal gland (primary hyperaldosteronism), or from systemic pathology (secondary hyperaldosteronism)

TABLE 2-34. Summary of Adrenal-Related Hormones

Adrenal Cortex	Function
Aldosterone	Release stimulated by the renin-angiotensin axis. Acts at the level of the kidney to retain sodium (and thus water) and excrete potassium. Produced in the zona glomerulosa.
Cortisol	Glucocorticoid that functions as a stress hormone. Promotes glycogen formation in the liver and catabolism of fatty acids for energy. Release is stimulated by ACTH. Produced in the zona fasciculata.
Androgenic steroids	Sex hormone that results in development of male sexual characteristics (hair growth and muscle mass). Produced in the zona reticulata.
Adrenal Medulla	**Function**
Epinephrine	Stimulated by sympathetic neurons in response to stress. Strong vasopressor effects, as well as tachycardia, pupillary constriction, breakdown of glycogen, and immunosuppression. Increases myocyte excitability.
Norepinephrine	Stimulated by sympathetic neurons in response to stressors. Acts to increase heart rate, stimulate glucose release from glycogen stores, and prepare muscles for response ("fight-or-flight" hormone).

- **Primary hyperaldosteronism (Conn's syndrome):** Caused by an aldosterone-secreting adrenal tumor; symptoms include hypertension, hypernatremia, hypokalemia, metabolic alkalosis, and **low** plasma renin.
- **Secondary hyperaldosteronism:** Occurs when the BP-sensing apparatus in the kidneys perceives a depleted intravascular volume despite euvolemia. Associated with renal artery stenosis, chronic renal failure, congestive heart failure, cirrhosis, and nephrotic syndrome; serum plasma rennin will be **elevated**.

Addison's Disease

Condition resulting from primary adrenal failure with subsequent loss of adrenal hormones. Classically presents with skin hyperpigmentation, hypotension (secondary to decreased aldosterone production), fatigue, weakness, salt craving, nausea, and vomiting.

- **Skin hyperpigmentation:** The pituitary senses decreased adrenal hormone levels and stimulates **increased ACTH** production. Leads to increased MSH produced concomitantly with ACTH; increased MSH causes hyperpigmentation.
- **Lab studies:** May show hyponatremia and hyperkalemia.

Adrenal Medullary Tumors

Tumors that arise from the adrenal medulla. Result in overproduction of medullary hormones (epinephrine and norepinephrine). There are two major medullary tumors with patient age determining the most likely etiology:

- **Pheochromocytoma:** Cells of origin are chromaffin cells (derived from the neural crest). Most common tumor arising from the adrenal medulla in **adults**. Presents as symptomatic hypertension in young to middle-aged patients. Elevated urinary catecholamines suggest the diagnosis.
- **Neuroblastoma:** Small round blue cell tumor of **children** (neural crest origin). Most common neoplasm in **infants**. Occurs in the adrenals, but

may also be seen in the abdomen, retroperitoneal ganglia, or cervical and thoracic regions. Urinary catecholamines are elevated. Also presents with symptomatic hypertension.

Multiple Endocrine Neoplasia

All the MEN syndromes are inherited in an autosomal dominant fashion. They are divided into three categories based on the endocrine glands involved:

- **MEN 1 (Wermer's syndrome):** Tumors of the 3 Ps: Pancreas, Pituitary, and Parathyroid. May present with kidney stones secondary to hyperparathyroidism and GI ulcers secondary to gastrin-producing pancreatic adenomas (gastrinomas) which cause Zollinger-Ellison syndrome.
- **MEN 2 (Sipple's syndrome):** Medullary thyroid carcinoma, pheochromocytoma, and parathyroid adenoma.
- **MEN 3 (formerly MEN type 2B):** Medullary thyroid carcinoma, pheochromocytoma, and oral and GI mucosal neuromas (ganglioneuromatosis).

SUMMARY OF THYROID-RELATED HORMONES

See Table 2-35.

Hypothyroidism

Inadequate production of thyroid hormone; may be due to primary thyroid failure or secondary due to pituitary or hypothalamus pathology. See Table 2-36.

- **Classic symptoms:** Cold intolerance, fatigue, weight gain, decreased appetite, constipation, muscle weakness, menorrhagia, prolonged relaxation of deep tendon reflexes, facial/periorbital myxedema, dry cool skin, hair loss, and brittle hair and nails.
- **Psychological effects:** Depression and poor concentration.
- **Lab studies:** Decreased T_4 and elevated TSH.

Hyperthyroidism

Thyrotoxicosis is a state of excessive thyroid production secondary to a number of causes including malignancy, autoimmune, and ectopic production of thyroid hormones or TSH. See Table 2-37.

TABLE 2-35. Summary of Thyroid-Related Hormones

HORMONE	DESCRIPTION
Thyroid-stimulating hormone (TSH)	Produced by the pituitary. Stimulates the thyroid to produce T_3 and T_4, which in turn provides negative feedback to the pituitary.
T_3 (triiodothyronine)	Produced by the thyroid gland in response to TSH. Comprises 20% of thyroid output. More potent than T_4.
T_4 (thyroxine)	Produced by the thyroid gland in response to TSH. Comprises 80% of thyroid output. T_4 converted to T_3 by peripheral tissues.
Calcitonin	Secreted by C cells of the thyroid gland. Acts to decrease serum levels of calcium by decreasing calcium reabsorption from bone.

TABLE 2-36. Common Causes of Hypothyroidism

PRIMARY CAUSES	
Hashimoto's thyroiditis	Autoimmune in origin. Most common cause in the U.S. Antimicrosomal and antithyroglobulin antibodies confirm the diagnosis.
Subacute (de Quervain's) thyroiditis	Self-limited hypothyroidism following a flulike illness. May have elevated ESR and a tender thyroid gland. Believed to be viral in origin.
Iodine deficiency	Most common cause in the developing world. Iodine is essential to thyroid hormone with deficiency leading to hypothyroidism.
Riedel's thyroiditis	Rare disease in which thyroid tissue is chronically replaced by fibrosis.
Lithium toxicity	Lithium may cause hypothyroidism.
Surgical resection and ^{131}I treatment	Surgical removal or medical destruction may cause hypothyroidism.
Congenital hypothyroidism	Most commonly due to a mother taking supplementary thyroid hormone. Children may develop profound neurologic delay known as **cretinism** unless rapidly corrected.
SECONDARY CAUSE	
Sheehan's syndrome	Postpartum pituitary necrosis secondary to postpartum hemorrhage.

- **Classic symptoms:** Weight loss, heat intolerance, excessive sweating, palpitations, fatigue, weakness, diarrhea, oligomenorrhea, hyperreflexia, warm skin, and tachycardia.
- **Psychological effects.** Nervousness, anxiety, and irritability.
- **Lab studies.** Increased T_4 and decreased TSH.

TABLE 2-37. Common Causes of Hyperthyroidism

Graves' disease	Most common cause in the U.S. Autoimmune in nature. Proptosis (apparent bulging of eyes from the orbits) is pathognomonic. Mechanism is anti-TSH-receptor antibodies that bind the TSH receptor at the thyroid, mimicking TSH and activating the thyroid gland to produce thyroid hormone.
Thyroid adenoma	A single, benign neoplasm that secretes thyroid hormone autonomously, independent of the influence of TSH.
Toxic multinodular goiter	The second most common cause of hyperthyroidism in the developed world. Common in elderly people and locales where iodine deficiency is endemic. While an adenoma is one large autonomous nodule, TMG is several small autonomous nodules.
Thyroid carcinoma	Certain thyroid cancers may produce thyroid hormone. See detailed description below.
Struma ovarii	This is a very rare condition in which ectopic thyroid tissue develops as part of an ovarian tumor, causing hyperthyroidism.
Amiodarone	A well-recognized toxicity of the drug amiodarone is hyperthyroidism. Amiodarone may also cause hypothyroidism.

Thyroid Carcinoma

Thyroid carcinoma may be either benign or malignant. Classically presents with a palpable nodule or an enlarging neck mass (may cause dysphagia). The mass is usually unilateral; bilateral masses are more likely toxic multinodular goiter. Some thyroid neoplasms secrete functional hormones, which can cause hormone-specific symptoms. Patients with a **history of neck irradiation** are at increased risk. Divided into several categories based on histology:

- **Papillary thyroid cancer:** Most common type of thyroid cancer, characterized by papillary projections into gland-like spaces. **Psammoma bodies** and **ground-glass appearance** are classic. Relatively good prognosis.
- **Follicular thyroid cancer:** Characterized by uniform follicles; second most common type of thyroid cancer; poorer prognosis than the papillary type, but still fairly curable.
- **Medullary thyroid cancer:** Originates from C cells of the thyroid which produce **calcitonin**. Tumor may present due to effects of excess calcitonin, leading to hypocalcemia. Associated with MEN 1 and MEN 2.
- **Anaplastic thyroid cancer:** Tends to occur in the elderly. Extremely aggressive tumor with exceedingly poor prognosis.
- **Thyroid lymphoma.** Fairly rare; tends to arise in patients with a history of Hashimoto's thyroiditis.
- **Benign thyroid adenoma:** Most often occurs as a solitary nodule. May lead to hyperthyroidism.

PARATHYROID-RELATED HORMONES AND HORMONES ASSOCIATED WITH CALCIUM METABOLISM

See Tables 2-38 and 2-39.

TABLE 2-38. Hormones Associated with the Parathyroids and Calcium Metabolism

HORMONE	FUNCTION
Parathyroid hormone (PTH)	Main regulator of calcium in the body. Acts at the level of bone to increase calcium resorption by osteoclasts, calcium resorption and phosphate excretion at the kidney, and synthesis of vitamin D, thus increasing GI absorption of calcium. Low serum calcium stimulates PTH release.
Vitamin D	Acts at the level of the intestines to increase calcium absorption. Synthesized in the body via a process of hydroxylation in response to PTH.
Calcitonin	Acts to decrease serum levels of calcium by decreasing calcium reabsorption from bone. Secreted by C cells of the thyroid gland.
Parathyroid hormone-related peptide (PTHrP)	Parathyroid-related peptide. Produced ectopically by some types of cancer (i.e., squamous cell lung cancer). Not made by the parathyroid glands or under the control of normal calcium homeostasis mechanisms.

TABLE 2-39. Pancreatic-Related Endocrine Hormones

Hormone	Function
Insulin	Causes decreased serum glucose via cell uptake. Produced by beta cells of the pancreas.
Glucagon	Increases serum glucose via breakdown of cell glycogen. Produced by alpha cells of the pancreas.
Somatostatin	Acts to suppress release of GI hormones. Inhibits insulin and glucagon release. Produced by pancreas, hypothalamus, stomach, and intestine.
Gastrin	Stimulates parietal cells to secrete hydrochloric (gastric) acid. Produced mainly in G cells of pyloric antrum of stomach, small intestine, and to a limited extent in the pancreas.
Vasoactive intestinal peptide (VIP)	Secreted by pancreas and other sites to assist digestion by stimulating pancreatic bicarbonate release, inhibiting gastrin release, and dilating GI-related blood vessels.

DIABETES MELLITUS TYPE 1

Insulin-Dependent Diabetes Mellitus

Failure of insulin synthesis by the pancreatic beta cells thought to be caused by autoimmune destruction of islets leading to impaired serum glucose regulation. Usually presents early in life (usually prior to age 30). Less common and less influenced by genetic factors than DM-2.

- **Presentation:** Polydipsia, polyuria, and weight loss despite increased appetite related to hyperglycemia and failure of utilization of glucose leading to ketosis. Ketosis is classically associated with a **fruity odor** to the breath.
- **Management:** Requires insulin replacement therapy.
- **Genetic associations:** Predisposition associated with **HLA-DR3** and **HLA-DR4** alleles.
- **DKA:** A state of relative insulin deficiency preventing cells from using circulating glucose, while the endocrine system reacts by releasing more glucose. The body interprets this as a starvation state and starts to mobilize energy stored in fatty acids as ketone bodies (or ketoacids). Serum glucose levels are generally greater than 250 mg/dL, with serum pH of less than 7.30 and decreased bicarbonate. This leads to a high anion gap metabolic acidosis. The ketosis leads to polyuria, polydipsia, and alterations in mental status or coma. Common causes are new-onset DM-1, infection, or missed insulin treatments.

DIABETES MELLITUS TYPE 2

Non-insulin Dependent or Adult-Onset Diabetes Mellitus

More common than DM-1 and more likely to be associated with family history. Results from peripheral insulin resistance. Associated with increased levels of serum insulin, obesity, and sedentary lifestyle.

- **Presentation:** Obese patient with sedentary lifestyle.
- **Labs:** Elevated insulin and hemoglobin A_{1c}.
- **Management:** Diet and exercise and oral antidiabetic pharmacotherapy. May require insulin therapy.
- **Metabolic syndrome X:** DM-2, truncal obesity, hypertension, and hypercholesterolemia.
- **Nonketotic hyperosmolar coma:** Metabolic derangement characterized by hyperosmolarity resulting from increased serum glucose (often secondary to infection). This hyperglycemia leads to diuresis and fluid shifting into the intravascular space. Patients present with dehydration, altered mental status, and (possibly) neurologic deficits.

EFFECTS OF UNCONTROLLED DIABETES MELLITUS

Systemic changes will result from poorly controlled diabetes and hyperglycemia in both DM-1 and DM-2. They are broken down by organ and system (see Table 2-40).

TABLE 2-40. Systemic Effects of Uncontrolled DM

System	Effects
Kidney	Progression to chronic kidney disease secondary to diffuse glomerulosclerosis.
Heart	Greatly increased incidence of CAD, occurring at a much earlier age.
Vascular	Incidence of atherosclerosis and peripheral vascular disease is greatly increased. Lower extremity circulation problems may lead to venous stasis ulcerative disease.
Eyes	Cataract formation and proliferative retinopathy.
Peripheral nervous system	Peripheral neuropathy in stocking-and-glove distribution.
Liver	Fatty change of the liver.
Immune system	Immunocompromised state predisposing to increased infections.

PANCREATIC ISLET CELL TUMORS

Uncommon tumors of the pancreas arising from cells of neuroendocrine origin. They are classified according to the hormone they produce.

- **Insulinoma:** Tumors produce insulin. Symptoms are related to insulin excess and hypoglycemia (confusion, anxiety, stupor, and even coma). Most common islet cell tumor. Circulating levels of **C-peptide** (protein produced during insulin production) will be **increased**. Symptoms rapidly reverse with administration of glucose.
- **Gastrinoma:** Tumors produce gastrin. Often malignant and associated with **Zollinger-Ellison syndrome** (hypergastrinemia and significant peptic ulcer disease with numerous ulcers in the stomach and small bowel).
- **Glucagonoma:** Tumors produce glucagons. Causes hyperglycemia and symptoms of diabetes (polyuria, polydipsia, and weight loss). Known as **secondary DM.**
- **VIPoma:** Tumor produces VIP. Associated with **WDHA syndrome** (Watery Diarrhea, Hypokalemia, and Achlorhydria).

PITUITARY HORMONES

See Table 2-41.

TABLE 2-41. Hormones Produced by the Pituitary Gland

Anterior Pituitary	Function
TSH	Stimulates thyroid production of T_3 and T_4.
Follicle-stimulating hormone (FSH)	▪ Female: Stimulates follicular growth in the ovaries ▪ Male: Critical for spermatogenesis.
Luteinizing hormone (LH)	▪ Female: Triggers ovulation and maintains the corpus luteum to enable fertilization. ▪ Male: Stimulates Leydig cells to release androgens.
Adrenocorticotropic hormone (ACTH)	Stimulates adrenal cortex to produce cortisol, aldosterone, and sex hormones.
Growth hormone (GH)	Stimulates growth (especially in childhood) and maintenance of the immune system.
Prolactin	Stimulates enlargement of breast tissue during pregnancy and milk production postpartum.
Posterior Pituitary	**Function**
Antidiuretic hormone (ADH)	**Vasopressin.** Release triggered by serum osmolarity. Stimulates water reabsorption by the kidneys (concentrating the urine). Critical hormone for maintenance of serum osmolarity homeostasis.
Oxytocin	Stimulates uterine contractions during labor and breasts during breast-feeding.

DIABETES INSIPIDUS

Deficiency of ADH leading to polyuria, dehydration, and unquenchable thirst. Causes include neoplasm, head trauma, inflammation, and any other condition that damages the posterior pituitary.

- **Presentation:** Polyuria, thirst, and hypernatremia.

SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE (SIADH)

Overproduction of ADH, most commonly due to ectopic production of ADH by a neoplasm (i.e., small cell lung cancer). Leads to water retention and hyponatremia.

- **Presentation:** Symptoms of hyponatremia (mental status changes and inability to dilute the urine).
- **Lab studies:** Decreased serum osmolarity.

SHEEHAN'S SYNDROME

Pituitary necrosis in the postpartum female. During pregnancy the pituitary grows much larger than its normal size and requires increased blood delivery. If postpartum hemorrhage complicates delivery, the pituitary may not be adequately perfused, leading to necrosis.

- **Presentation:** Presents with panhypopituitarism and deficiency of all of the pituitary hormones. Most notable is the lack of ability to breast-feed and hypothyroidism.

ABNORMALITIES OF PITUITARY FUNCTION

See Table 2-42.

TABLE 2-42. Abnormalities with Pituitary Hormones and Resulting Manifestations

HORMONE	MANIFESTATION
↑ Prolactin	▪ Females: Amenorrhea and galactorrhea. ▪ Males: Impotence and galactorrhea.
Increased ADH	SIADH.
↑ GH	▪ Children: Gigantism. ▪ Adults: Acromegaly.
↓ GH	▪ Children: Growth retardation and dwarfism. ▪ Adults: Increased insulin sensitivity.
↑ ACTH	Cushing's disease.
↓ ACTH	Secondary adrenal failure (will not have hyperpigmentation associated with Addison's disease).
↓ TSH	Secondary hypothyroidism.

CARCINOID TUMOR

Rare tumor of GI tract neuroendocrine cells. May be located anywhere in the GI tract or lungs with the appendix being the most common location. Secretes high levels of serotonin (5-HT) which is metabolized in the liver to 5-hydroxyindoleacetic acid (5-HIAA). Look for elevated levels of 5-HIAA in serum and urine.

- **Presentation:** May present with carcinoid syndrome or symptoms of intestinal or bowel obstruction based on the location of the tumor. Lung carcinoids may present on chest X-ray.
- **Carcinoid syndrome:** Elevated serotonin leading to diarrhea, cutaneous flushing, wheezing, and right-sided valvular lesions.

CHAPTER 3

Gastrointestinal

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Embryology

OVERVIEW OF GASTROINTESTINAL SYSTEM DEVELOPMENT

The primitive GI tract begins to form around the fourth week of development in a complex series of steps. Understanding the following sequence of events will aid in understanding the pathologic conditions that may ensue following abnormal development.

CLINICAL CORRELATION

The vitelline duct joins the yolk sac at the junction of the cranial and caudal limbs of the midgut loop. It persists as Meckel's diverticulum in 2% of the population.

Fourth Week

Primitive gut begins to develop:

- Endoderm becomes intestinal epithelium and glands.
- Mesoderm becomes connective tissue, muscle, and wall of intestine.

KEY FACT

The midgut loop rotates a total of 270° counterclockwise around the axis of the SMA before it reaches its final fixed position in the abdomen.

Fifth Week

The intestine elongates and the midgut loop herniates through the umbilicus. This midgut loop has cranial (near the head) and caudal (near the tailbone) limbs:

- The cranial limb becomes the distal duodenum to the proximal ileum.
- The caudal limb becomes the distal ileum to the proximal two-thirds of the transverse colon.

Tenth Week

The midgut loop returns to the abdominal cavity in its final fixed position after rotating a total of 270° counterclockwise around the axis of the superior mesenteric artery (SMA).

CONGENITAL MALFORMATIONS OF THE GI TRACT

Omphalocele

The result of failure of bowel to return to the abdomen following the herniation of abdominal contents into the base of the umbilical cord during the fifth week of embryonic life. The herniated intestine is covered by peritoneal membrane. Most commonly affects children of mothers at the extremes of reproductive age.

Presentation

During the second-trimester ultrasound or when a herniated sac is found at birth. The associated anomalies include:

- **Beckwith-Wiedemann syndrome:** Gigantism, macroglossia, umbilical defect, and hypoglycemia.
- **Pentalogy of Cantrell:** Omphalocele, diaphragmatic hernia, cleft sternum, absent pericardium, and intracardiac defects.

Diagnosis

Herniated sac can be visualized by ultrasound in 95% of cases.

- **α-Fetoprotein (AFP):** Serum values are elevated in 70% of cases.

Treatment

Close monitoring of the fetus during pregnancy and prompt treatment at delivery. Surgical reduction of the herniated contents.

Gastroschisis

A full-thickness abdominal wall defect caused by vascular injury during development allowing small or large bowel to escape the abdominal cavity. No protective peritoneal membrane covers the herniated intestine. Gastroschisis is more common in children born to women < 20 years of age.

Presentation

Most often seen in the second-trimester ultrasound in combination with an elevated serum AFP. Extruded abdominal contents are noted at birth. The defect is usually to the right of the abdominal midline.

Diagnosis

Herniated bowel resembles cauliflower on ultrasound. Intestinal atresia may also be seen, as well as elevated serum **AFP.**

Treatment

Surgical correction of the abdominal wall defect with return of the herniated contents to the abdomen. **Artificial covering** may be used to minimize heat/fluid loss and assist with **temperature regulation** (exposed bowel causes increased heat loss). **Nasogastric tube, broad-spectrum antibiotics,** and **total parenteral nutrition** (TPN).

Intestinal Malrotation

Develops as a result of abnormal **midgut** development and rotation, which in turn causes anomalous positioning of the small intestine, cecum, and ascending colon.

- **Cecum** remains in the RUQ or in the left abdomen and the **duodenojejunal** junction remains to the right of the midline.
- The aberrant peritoneal attachments (Ladd's bands) can cause partial or complete **obstruction** of the duodenum (this can present in infancy or as late as early adulthood).
- **Midgut volvulus** occurs when the malrotated intestine twists on the axis of the **SMA,** compromising intestinal blood flow.

Presentation

Midgut volvulus may occur at any time during the first year of life and presents with sudden onset of severe **bilious** emesis, abdominal pain and distention, and rectal bleeding. Delay in recognition and treatment can lead to significant intestinal necrosis, resulting in shock and loss of viable intestine. Resection of the small bowel may lead to **short gut syndrome.**

Diagnosis

- **Abdominal X-ray:** Variable; may be normal (early) or gasless.
- **Upper GI study:** Distal duodenal obstruction; may have a corkscrew appearance.
- **Ultrasound:** May show twisted superior mesenteric vessels ("whirlpool sign").

Treatment

Urgent surgery consisting of Ladd's procedure (counterclockwise volvulus reduction, lysis of adhesive bands, bowel resection if needed, appendectomy, and repositioning of the small intestine to the RLQ and the cecum to the LLQ). May lead to short-bowel syndrome or death if treatment is delayed.

KEY FACT

The peritoneal attachments to the lateral abdominal wall normally fix the cecum retroperitoneally. In malrotation, they cross over the duodenum to reach the high, malrotated cecum, and are called Ladd's bands.

? CLINICAL CORRELATION

Associated anomalies occur in 70% of patients and include:

- Other abdominal defects.
- Situs inversus, septal defects, transposition of the great vessels, and anomalous systemic or pulmonary venous return.
- Asplenia or polysplenia.

KEY FACT

Bilious emesis in a neonate is presumed to be midgut volvulus until proven otherwise!

KEY FACT

Women who use vasoactive substances (e.g., cigarettes or medications) during the first trimester are three times as likely to have a child with duodenal atresia.

Duodenal Atresia

During weeks 6 and 7 of development, the duodenum becomes completely obstructed by proliferating endoderm. Failure of the duodenum to recanalize by week 10 results in duodenal atresia.

Presentation

The newborn may be small for gestational age. Symptoms of obstruction (vomiting and abdominal distention) appear within 48 hours of birth. The vomiting may be bilious. Physical exam may show an abdominal mass and jaundice if obstruction of the biliary system occurs.

Associated anomalies include **Down's syndrome.** Of those affected, 30% also have:

- **Gastroschisis.**
- **Imperforate anus or other intestinal atresia.**
- **Cardiac, renal, and vertebral malformations.**

Diagnosis

Duodenal atresia may be detected by prenatal ultrasound or may not become apparent until birth.

- **Prenatal ultrasound:** Polyhydramnios from inability to swallow amniotic fluid (seen in 50%) or dilated bowel.
- **Abdominal radiograph:** "Double-bubble" sign due to dilation of the stomach and proximal duodenum.

Treatment

Definitive treatment is **duodenoduodenostomy** (anastomosis of the proximal and distal duodenum to bypass the obstruction) or **duodenojejunostomy.**

- **Preoperatively:** Nasogastric tube (to decompress the stomach), IV fluids (to maintain hydration), and correction of electrolyte abnormalities.
- **Postoperatively:** Nasogastric tube, IV fluids, and TPN until oral feeds can be started.

Pyloric Stenosis

Pyloric stenosis is of idiopathic etiology and develops as a result of congenital elongation and thickening of the pylorus, which in turn results in obstruction of the gastric outlet. Most commonly seen in firstborn males.

Presentation

Usually at 3–6 weeks of age, presenting with difficulty feeding followed by projectile, **nonbilious** vomiting. **Notably absent are signs of illness** (fever, diarrhea). Affected children are often hungry after the episodes.

Diagnosis

Physical exam classically shows a palpable mass (described as an "olive") in the epigastric region. Lab tests may demonstrate a hypochloremic, metabolic alkalosis secondary to loss of HCl in emesis and hypokalemia late in presentation. **Ultrasound** (see Figure 3-1) shows an elongated and hypertrophic pylorus. **Barium studies** show:

- **String sign:** Seen on barium swallow when barium moves through the pylorus.
- **Shoulder sign:** The pylorus bulges into the antrum of the stomach.
- **Double tract sign:** Parallel streaks of barium seen in the narrow pylorus.



FIGURE 3-1. Pyloric stenosis. A 6-week-old infant with recurrent nonbilious vomiting. Image reveals distended stomach with a thickened pylorus indicative of pyloric stenosis. (Image courtesy of PEIR Digital Library [http://peir.net].)

TREATMENT

Correction of lab abnormalities and hydration status prior to surgery.

- **Pyloromyotomy** (longitudinal incision through the muscle of the pylorus with dissection to the submucosa) is definitive therapy.

Anatomy

ABDOMINAL WALL

The abdomen is defined as the region of the trunk that lies between the diaphragm (superiorly) and the inlet of the pelvis (inferiorly).

Surface Anatomy

Landmarks of the abdominal wall are shown in Figure 3-2.

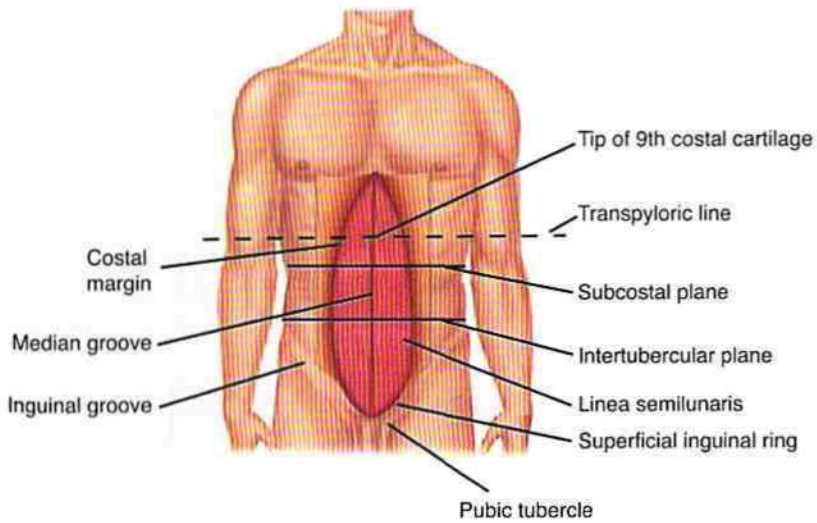


FIGURE 3-2. Landmarks of the abdominal wall.

Linea Alba

A vertical fibrous band that extends from the symphysis pubis to the xiphoid process and lies in the midline. It is formed by fusion of the aponeuroses of the muscles of the anterior abdominal wall and is represented on the surface by a median groove.

Linea Semilunaris

Defines the lateral edge of the rectus abdominis muscle and crosses the costal margin at the tip of the ninth costal cartilage.

Inguinal Groove

Formed by the inguinal ligament. It lies beneath a skin crease in the groin and is formed by the rolled-under margin of the aponeurosis of the external oblique muscle.

ABDOMINAL PLANES AND REGIONS

Vertical lines and horizontal planes are used to describe the sites of abnormal features and disease processes within the abdominal cavity. In this way, the abdomen is divided into four quadrants or nine regions, usually projected onto the anterior abdominal wall.

Vertical Lines

Each line passes through the midpoint of the anterior superior iliac spine or the symphysis pubis.

Transpyloric Plane

So called because it cuts through the pylorus and represents a **horizontal plane** that passes through the tips of the ninth costal cartilages on each side. It lies at the level of L1.

- Identifies the pylorus of the stomach, the duodenojejunal junction, the neck of the pancreas, and the hila of the kidneys.

Subcostal Plane

Horizontal plane joining the lowest point of the costal margin on each side. It lies at the level of L3.

Intertubercular Plane

Horizontal plane joining the tubercles on the iliac crests. It lies at the level of L5.

CLINICAL CORRELATION

McBurney's point is located in the RLQ at two-thirds the distance from the umbilicus to the anterior superior iliac spine. Pain and tenderness from appendicitis is classically found at this spot.

Abdominal Regions

Anatomically, there are **nine** defined regions of interest (see Table 3-1). In clinical practice, however, these regions are defined imprecisely.

Abdominal Quadrants

The abdomen can be divided into **four** quadrants (see Table 3-2), using a horizontal line and a vertical line that intersect at the umbilicus.

TABLE 3-1. Contents of the Respective Abdominal Regions

Right Hypochondriac Region ▪ Liver and gallbladder ▪ (Kidney) and suprarenal gland ▪ Colon, hepatic flexure	**Epigastric Region** ▪ Liver ▪ (Transverse colon) ▪ Abdominal aorta and vena cava ▪ Pylorus and duodenum (first part)	**Left Hypochondriac Region** ▪ Stomach ▪ Spleen ▪ (Kidney) and suprarenal gland ▪ Colon, splenic flexure
Right Lumbar Region ▪ Kidney ▪ Colon, ascending ▪ Small intestine ▪ Duodenum (first part)	**Umbilical Region** ▪ (Transverse colon) ▪ Duodenum and pancreas ▪ Abdominal aorta and vena cava ▪ Small intestine ▪ Iliac vessels	**Left Lumbar Region** ▪ Kidney ▪ Colon, descending ▪ Pancreas ▪ Small intestine (jejunum)
Right Iliac Region ▪ Cecum ▪ Appendix ▪ Small intestine (ileum)	**Hypogastric Region** ▪ Distensible organs of the pelvis (e.g., bladder in infants or in adults when full; uterus after 12th week of pregnancy) ▪ Small intestine ▪ Iliac vessels ▪ Spermatic cords	**Left Iliac Region** ▪ Sigmoid colon ▪ Small intestine

Layers of the Abdominal Wall

The anterolateral abdominal wall is made up of:

- Skin
- Superficial fascia (fatty [Camper's] and membranous [Scarpa's])
- Deep fascia
- Aponeurosis
- External oblique muscle—lateral wall
- Internal oblique muscle—lateral wall
- Transversus abdominis muscle—lateral wall
- Transversalis fascia
- Extraperitoneal fat
- Parietal peritoneum

TABLE 3-2. Abdominal Quadrants

	RIGHT	LEFT
Upper	▪ Liver ▪ Gallbladder (fundus at tip of ninth costal cartilage, where the lateral border of the rectus abdominis muscle crosses the costal margin) ▪ Kidney and suprarenal gland ▪ Colon (hepatic) flexure and right transverse ▪ Duodenum with head of pancreas (part) ▪ Small intestine	▪ Stomach ▪ Spleen ▪ Pancreas ▪ Kidney and suprarenal gland ▪ Colon (splenic) flexure and left transverse ▪ Small intestine (jejunum)
Lower	▪ Colon (ascending) ▪ Cecum ▪ Appendix (including McBurney's point) ▪ Small intestine (ileum)	▪ Colon (descending and sigmoid) ▪ Small intestine

KEY FACT

During embryonic development, the testes and spermatic cord (in males) and the round ligament of the uterus (in females) descend through the inguinal region.

KEY FACT

Failure of the processus vaginalis to obliterate leads to patent communication between the abdominal cavity and the scrotal sac.

MNEMONIC

Contents of the femoral triangle (from lateral to medial) include:
NAVEL

Nerve
Femoral **A**rtery
Femoral **V**ein
Empty space
Lymphatic

MNEMONIC

Venous near penis.
The vein is more medial than the artery.

Figure 3-3 shows the musculature, innervation, blood supply, and lymphatic drainage of the anterior abdominal wall.

Inguinal Canal

The inguinal canal is an oblique passage through the inguinal region and a site of inguinal hernias (both direct and indirect; see Figure 3-4).

Boundaries of the inguinal canal:

- **Deep inguinal ring:** Oval opening in the fascia transversalis lateral to the inferior epigastric vessels.
- **Superficial inguinal ring:** Triangular defect in the aponeurosis of the external oblique muscle, lateral to the pubic tubercle.
- **Anterior wall:** Aponeuroses of the external and internal oblique muscles.
- **Posterior wall:** Aponeuroses of the internal oblique and transverse abdominal muscles and fascia transversalis.
- **Roof:** Internal oblique and transverse abdominal muscles.
- **Floor:** Inguinal and lacunar ligaments.

Femoral Triangle

The femoral triangle is the anatomic region of the upper inner thigh bounded by the following (see Figure 3-5):

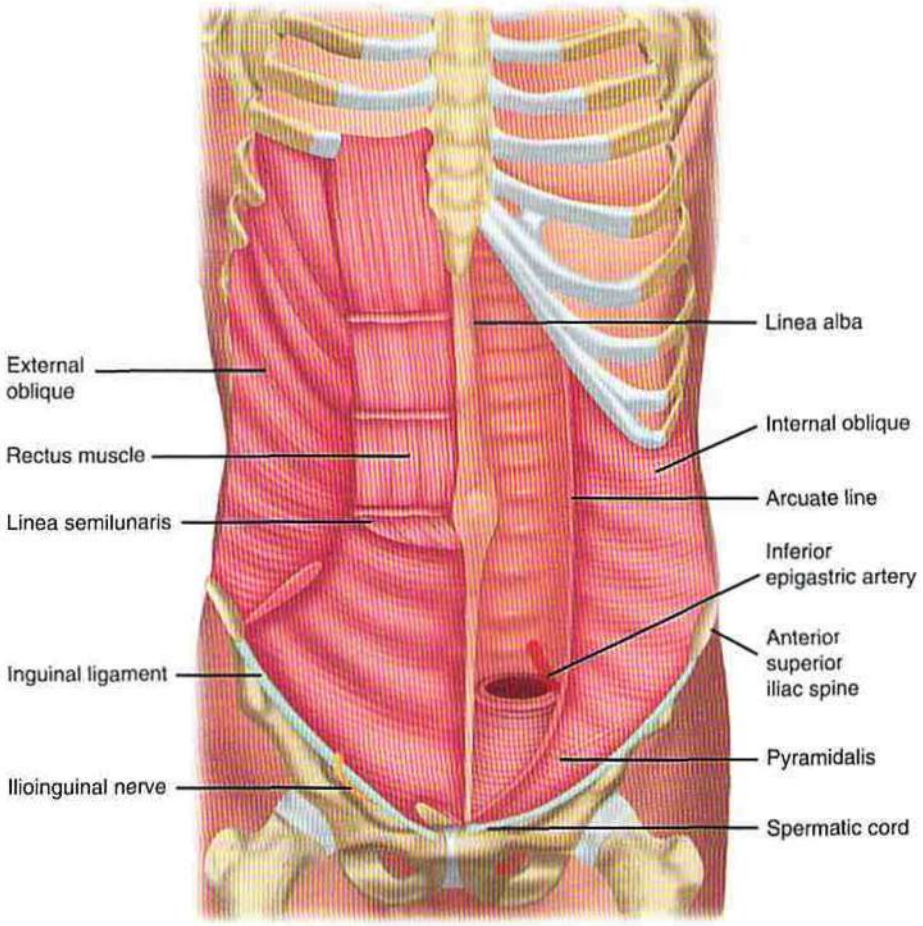


FIGURE 3-3. Anterolateral abdominal wall.

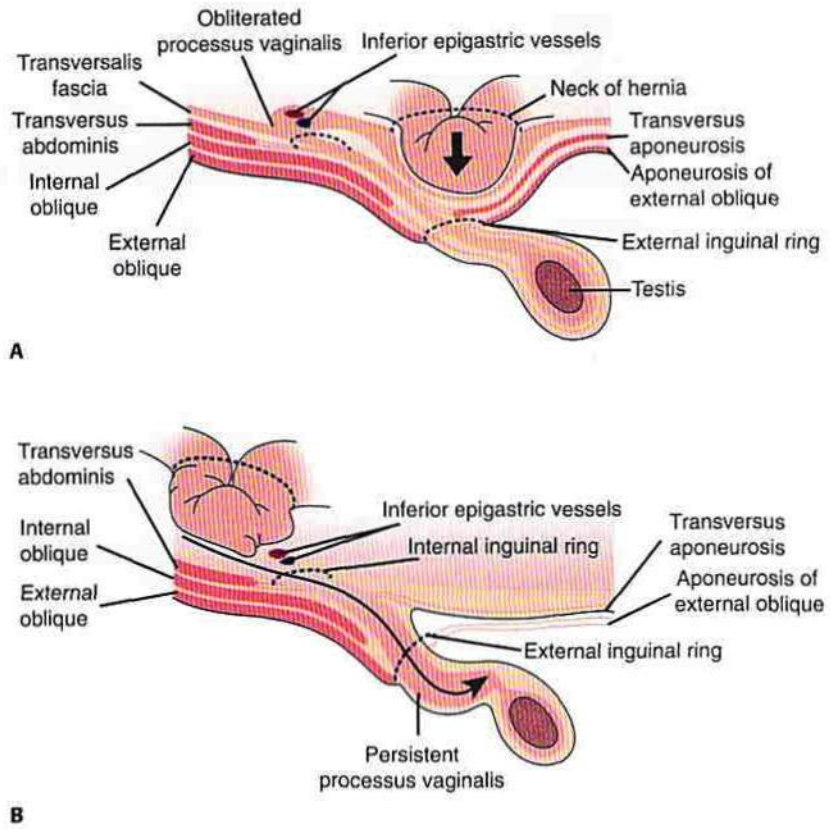


FIGURE 3-4. Inguinal hernias. Direct (A) and indirect (B). (Modified, with permission, from Tintinalli JE, Kelen GD, Stapczynski JS, et al., eds, *Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 6th ed*, New York: McGraw-Hill, 2004: 528)

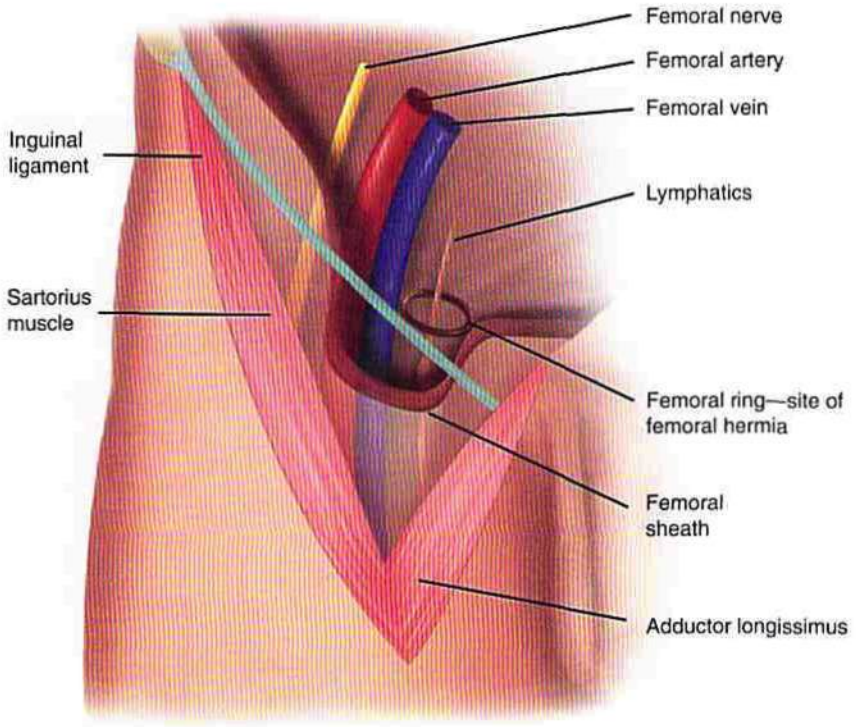


FIGURE 3-5. Femoral canal. Femoral hernias bulge through the femoral ring, medial to the femoral vein.

FLASH FORWARD

Direct inguinal hernia: Protrudes **medial** to the epigastric artery and vein.
Indirect inguinal hernia: Protrudes **lateral** to the epigastric artery and vein.
Femoral hernia: Distinguish from direct and indirect inguinal hernias (protrudes **below** the inguinal ligament in the femoral triangle).

KEY FACT

Remember that third spacing includes **all non-intravascular** space where edema and fluid can accumulate. It is **not** limited to the intraperitoneal space.

CLINICAL CORRELATION

Ascites is an accumulation of **extra fluid** in the peritoneal cavity (common causes include liver failure, right sided heart failure, ovarian cancer).
Pneumoperitoneum is air or other gas in the peritoneal cavity (intestinal or stomach perforation, or intentional insufflation for laparoscopy).

- **Superiorly:** Inguinal ligament
- **Laterally:** Sartorius muscle
- **Medially:** Adductor longus muscle

PERITONEUM AND ABDOMINAL VISCERA

The abdominal cavity contains several important structures in addition to the abdominal organs.

Abdominal and Pelvic Peritoneum

The peritoneum is a serous membrane that covers the abdominal organs (see Table 3-3) and is composed of **two layers**: the parietal and visceral peritoneum.

Parietal Peritoneum

The outer membrane that lines the deep surface of the abdominal walls and the inferior surface of the diaphragm.

- The **nerve supply** originates from the nerves of the surrounding abdominal muscles and skin, **intercostal** and **phrenic** nerves in the **abdominal** region, and **obturator** nerve in the **pelvic** region.

Visceral Peritoneum

The membrane that directly covers the abdominal organs. There is no somatic nerve supply to the visceral peritoneum.

Peritoneal Cavity

The peritoneal cavity is a narrow, "potential" space between the opposing layers of the peritoneum, and it reflects the rotation of the GI tract during its embryonic development.

- **Normally, no space** exists between the parietal and visceral peritoneum (only ~50 mL of serous peritoneal fluid).
- In **pathologic conditions** (e.g., ascites), more fluid can accumulate between the two layers of peritoneum. This phenomenon of extravascular fluid accumulation is known as **third spacing.**

TABLE 3-3. Intraperitoneal and Extraperitoneal Viscera

Intraperitoneal Viscera	Extraperitoneal Viscera
Stomach	Parts two, three, and four of the duodenum
First part of duodenum	Ascending and descending colon
Jejunum, ileum, cecum, appendix	Distal rectum
Transverse and sigmoid colon	Head, neck, and body of pancreas
Proximal rectum	Abdominal aorta
Liver and gallbladder	Inferior vena cava
Tail of pancreas	Kidneys, ureters, and adrenal glands
Spleen	

As a "potential" space, the peritoneal cavity can be divided into the greater and lesser peritoneal sacs.

- The **lesser sac** (omental bursa) is a pouch of peritoneum that lies posterior to the stomach, liver, and lesser omentum. It communicates with the greater sac through the **epiploic foramen** (omental or **Winslow's** foramen).
- The **greater sac** encompasses the rest of the peritoneum and is subdivided by the transverse mesocolon into the supracolic compartment (above), and the infracolic and pelvic compartments below the mesocolon.

KEY FACT

The supracolic compartment is divided by the falciform ligament.
The subphrenic recess is the area to the right of the falciform ligament between the liver and kidney.

Mesentery

Mesentery is a double layer of peritoneum that wraps around abdominal organs, includes blood vessels, and attaches the organ to its major blood supply.

ARTERIAL SUPPLY OF THE GI TRACT

The arterial blood supply of the GI tract is derived from the abdominal aorta.

Abdominal Aorta

The abdominal aorta is the portion of the descending aorta inferior to the diaphragm. It gives off **three large branches** from the anterior surface that supply blood to the GI organs: the **celiac trunk**, the **SMA**, and the **inferior mesenteric artery (IMA)** (see Figure 3-6). The abdominal aorta also gives rise to the **inferior phrenic, middle suprarenal, renal,** and **gonadal** arteries.

- The abdominal aorta divides into the **left** and **right common iliac** arteries, which then descend into the pelvis.

CLINICAL CORRELATION

Gradual occlusion at the bifurcation of the abdominal aorta may result in **claudication** and **impotence.**

Celiac Trunk

The celiac trunk is the first large branch off the abdominal aorta (see Figure 3-7), located just inferior to the diaphragm and the phrenic arteries. It immediately gives off three main branches: the **left gastric** artery, the **splenic** artery,

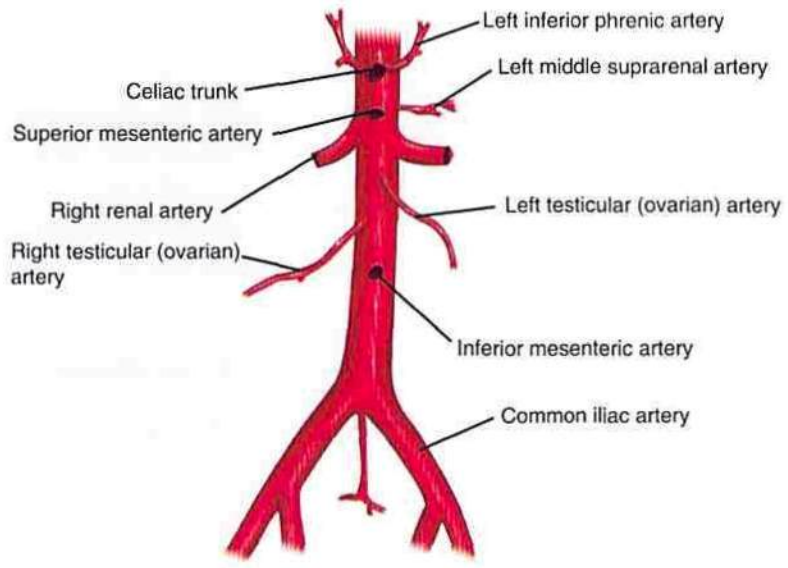


FIGURE 3-6. Abdominal aorta and its branches.

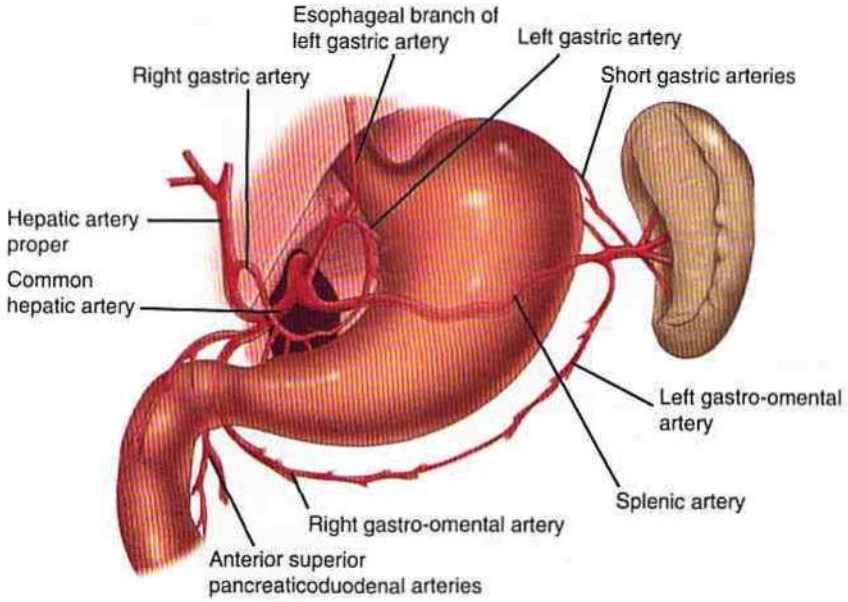


FIGURE 3-7. Celiac trunk.

and the **common hepatic** artery, all supplying structures that derive from the **foregut** (see Table 3-4).

SMA

Supplies the **derivatives** of the **midgut** (see Table 3-5).

IMA

Supplies the **hindgut derivatives**: the distal third of the transverse colon, the descending colon, the sigmoid colon, and the superior portion of the rectum.

- Its branches include:
  - The **left colic artery**, supplying the left transverse colon and descending colon.
  - The **sigmoid** and **superior rectal** arteries, supplying the organs for which they are named.

TABLE 3-4. Branches of the Celiac Trunk

PRIMARY BRANCHES	SECONDARY BRANCHES	ORGANS SUPPLIED (FOREGUT DERIVATIVES)
Left gastric artery.	Esophageal branch of the left gastric artery.	Esophagus, stomach.
Splenic artery.	Dorsal pancreatic artery, short gastric arteries, left gastro-omental (gastroepiploic) artery.	Stomach, pancreas, spleen.[a]
Common hepatic artery.	Gastroduodenal artery, right gastric artery, hepatic artery proper.	Upper duodenum, liver, gallbladder, pancreas.

[a]The spleen is not a foregut derivative. It is of mesodermal origin.

TABLE 3-5. Organs Supplied by the Branches of the SMA

Branch	Organs Supplied
Inferior pancreaticoduodenal arteries	Head of the pancreas; second through fourth portions of the duodenum
Middle colic artery	Transverse colon
Right colic artery	Ascending colon
Intestinal arteries (jejunal and ileal arteries)	Jejunum and ileum
Ileocolic artery (branches into the colic and ileal arteries; the ileal branch gives rise to the appendicular artery)	Ileum, cecum, appendix

VENOUS DRAINAGE OF THE GI TRACT

Three major venous systems are responsible for the venous drainage of the GI tract: the azygos vein, IVC, and hepatic portal system.

Azygos Venous System

The azygos venous system is an anastomosis between the superior and inferior vena cavae. It is composed of the **hemiazygos vein** (on the left side of the vertebral column), which drains the blood from the left renal vein into the **azygos vein** (on the right side of the vertebral column), which ultimately drains the blood from the IVC to the SVC.

Inferior Vena Cava (IVC) Venous System

The IVC venous system (see Figure 3-8) is responsible for draining the blood from the lower half of the body (below the diaphragm) into the right atrium.

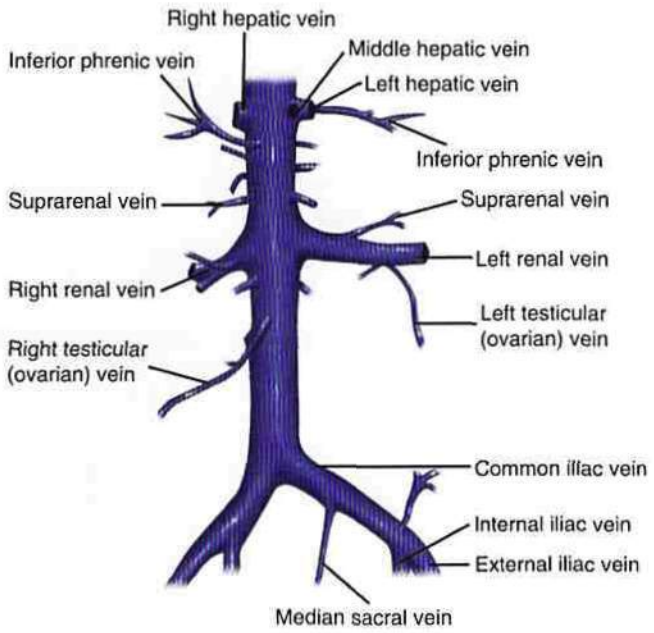


FIGURE 3-8. Inferior vena cava.

CLINICAL CORRELATION

Left testicular varicocele in the male may occur as a result of occlusion of the **left renal** artery.

MNEMONIC

To remember the veins that contribute to the portal vein:

The **SUPERIOR** **M**en left a gift of **S**plendid **P**ort.

Superior **M**esenteric
Splenic
Portal vein

- Drainage patterns:
  - Formed by the left and right common iliac veins at L5.
  - The **right** gonadal and suprarenal veins drain directly into the IVC; their **left** counterparts drain into the left renal vein, which then drains into the IVC.

Portal Venous System

The portal venous system is centered on the portal vein, which drains blood from the spleen, intestine, and colon into the liver, and is formed by the **superior mesenteric** and **splenic veins** posterior to the neck of the pancreas. The **portal** vein is situated in the hepatoduodenal ligament.

The portal vein transports nutrient- (and toxin-) rich blood from the GI tract as well as products of lysed RBCs from the spleen to the sinusoids of the liver. The IVC is responsible for the venous drainage of the liver via the hepatic veins. The intraluminal pressure is higher in portal vein than in the IVC.

Portal to IVC Anastomoses (Collaterals)

Pathologies that cause portal hypertension lead to the use of collateral intra-abdominal venous flow pathways (anastomoses; see Figure 3-9).

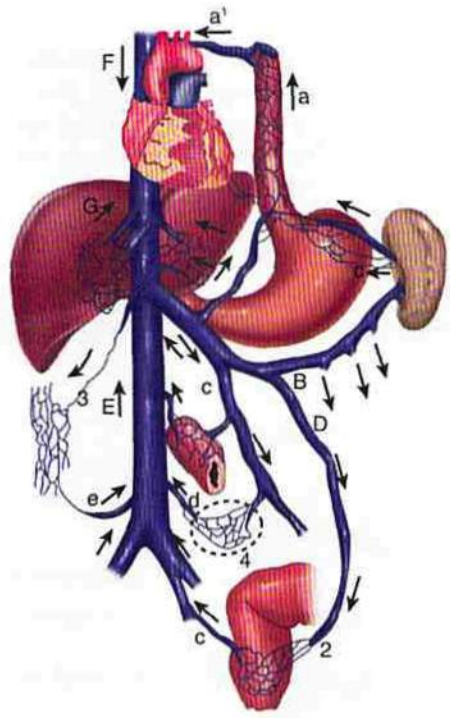


FIGURE 3-9. Intra-abdominal venous flow pathways leading to engorged veins (varices) from portal hypertension. 1 = coronary vein; 2 = superior hemorrhoidal veins; 3 = paraumbilical veins; 4 = veins of Retzius; 5 = veins of Sappey; A = portal vein; B = splenic vein; C = superior mesenteric vein; D = inferior mesenteric vein; E = inferior vena cava; F = superior vena cava; G = hepatic veins; a = esophageal veins; a^1 = azygos system; b = vasa brevia; c = middle and inferior hemorrhoidal veins; d = intestinal; e = epigastric veins. (Modified, with permission, from Brunicardi FC, Andersen DK, Billiar TR, *Schwartz's Principles of Surgery*, 8th ed, New York: McGraw-Hill, 2005: 1155.)

Esophagus

Coronary vein ↔ to the esophageal venous plexus.

- Portal hypertension from liver failure, such as cirrhosis, can cause esophageal varices.

Umbilicus

Paraumbilical vein ↔ to the superficial and inferior epigastric veins.

- Portal hypertension can cause the classic cirrhosis sign **caput medusa.**

Rectum

Superior rectal vein ↔ to the middle and inferior rectal veins.

- Enlarged internal hemorrhoids can occur following portal hypertension.

LYMPHATIC DRAINAGE OF THE GI TRACT

The end point of all lymphatic flow from the GI tract and its organs is the **thoracic duct,** which in turn empties into the venous system at the **junction** of the **left common carotid artery** and **left subclavian vein.**

- Before passing into the thoracic duct, the lymph from the GI tract passes through the **pre-aortic lymph nodes,** which can be divided into the **celiac, superior mesenteric,** and **inferior mesenteric nodes.**

KEY FACT

Lymphatic drainage from organs almost always follows the arterial supply. For example, lymphatic drainage from the foregut will pass through the celiac nodes (as the foregut supplied by the celiac trunk).

Peyer's Patches

Peyer's patches, known as gut-associated lymphoid tissue (GALT), are conspicuous aggregates of lymphoid tissue located throughout the lining of the digestive tract. They play a critical role in immune function by acting as the first line of defense against pathogens invading the gut. Large concentrations are typically found in the ileum and, in certain pathologic states such as inflammatory bowel disease (IBD), can proliferate to the point at which they are visible to the naked eye.

- Peyer's patches produce **secretory IgA.**
- **Lymphomas** can also arise from within Peyer's patches.

KEY FACT

Lymphadenopathy is often the first sign of GI infection or neoplasia.

NERVE SUPPLY OF THE GI TRACT

The GI tract has a rather complex nerve supply, divided into two major groups: extrinsic (parasympathetic and sympathetic innervation), and intrinsic (enteric) innervation.

Extrinsic Innervation

Extrinsic motor and sensory innervation is supplied by both sympathetic and parasympathetic nerves (see Figure 3-10).

Sympathetic Innervation

Arises at spinal cord levels **T5–L1.**

- The preganglionic fibers synapse with the prevertebral abdominal ganglia (**celiac, superior,** and **inferior mesenteric**).
  - The primary **preganglionic** neurotransmitter is **acetylcholine (ACh),** which interacts with the **nicotinic receptors** of the postganglionic nerves.

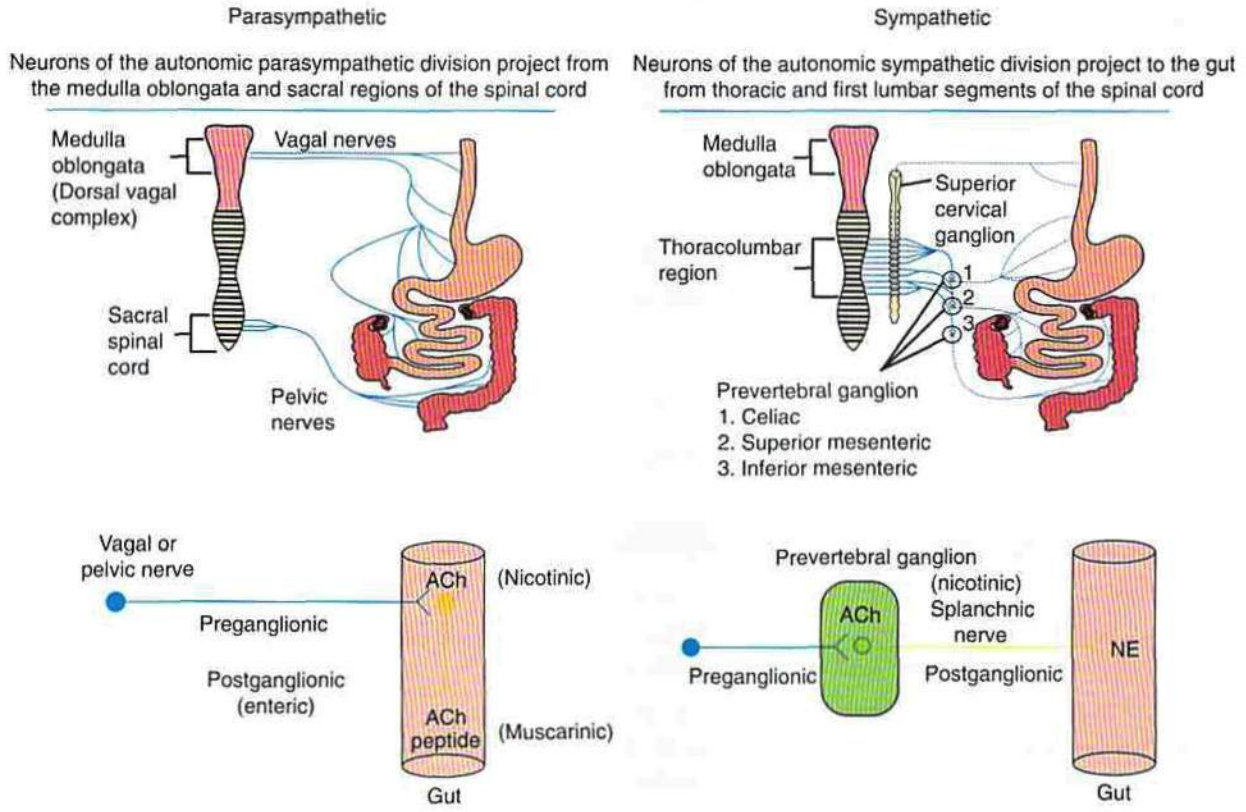


FIGURE 3-10. Extrinsic nervous system of the GI tract. ACh = acetylcholinesterase; NE = norepinephrine. (Modified, with permission, from McPhee SJ, Ganong WF, *Pathophysiology of Disease: An Introduction to Clinical Medicine, 5th ed*, New York: McGraw-Hill, 2006: 346.)

- The postganglionic fibers then spread to all parts of the gut via the **splanchnic nerves** and terminate on neurons in the enteric nervous system.
  - The primary **postganglionic** neurotransmitter is **norepinehrine,** which acts as an **inhibitory neurotransmitter** in the GI tract, **decreasing motility** as well as facilitating secretory and digestive functions.

PARASYMPATHETIC INNERVATION

Supplied by the vagus and pelvic nerves:

- The **vagus** nerve (CN X) provides both **parasympathetic afferent** and **efferent** stimuli to and from the esophagus, stomach, gallbladder, pancreas, entire small intestine, and the proximal half of the large intestine.
- **Pelvic nerves** arising at S2 and S3 innervate the distal half of the colon, entire sigmoid, and rectum.
  - Preganglionic fibers of the parasympathetic (vagus and sacral) nerves **synapse directly** in the enteric nervous system, releasing **ACh** and activating **nicotinic** receptors.
  - **Postganglionic fibers** only run in the wall of the organ they innervate and activate the **muscarinic** receptors (via ACh).
  - The parasympathetic system **increases** the activity level of the enteric nervous system.

MNEMONIC

The parasympathetic system allows one to **rest** and **digest** (via the **vagus** nerve).

Intrinsic Innervation

Also known as the **enteric nervous system,** or the "third division" of the autonomic nervous system. It is composed of a series of ganglionic nerve plexuses,

contained entirely within the gut wall and running from esophagus to anus. Enteric neurons use many neurotransmitters, most notably, **neuropeptides.**

The two principal components of the enteric nervous system are the **myenteric (Auerbach's)** plexus and the **submucosal (Meissner's)** nerve plexus (see Figure 3-11):

- The **myenteric (Auerbach's) nerve plexus** is located between the **outer longitudinal** and **inner circular muscle layers.** Its main function is to *coordinate motility along the full length of the gut wall.*
- The **submucosal (Meissner's) nerve plexus** is located in the **submucosa** between the innermost mucosal layer and the inner circular layer of smooth muscle. Its main function is to regulate secretions, blood flow, and absorption.

Visceral Sensation

Visceral sensory information from the gut is not usually consciously perceived.

- **Normal visceral sensation,** for the most part, is not perceived, except for sensations such as hunger and rectal distention.
- **Abnormal visceral sensation,** however, is perceived as diffuse **pain.**

Visceral Versus Parietal Pain

Due to the differential innervation of the viscera and the parietal peritoneum, visceral pain results in **cramping** pain, while parietal pain causes **sharp** pain.

- The pain fibers that originate in the **viscera** are transmitted via autonomic nerves, mainly sympathetic, **type C fibers,** which only transmit **colicky/cramping,** poorly localized types of pain.
- In contrast to the viscera and visceral peritoneum, the parietal peritoneum is innervated by extensions of the **peripheral spinal nerves,** which

CLINICAL CORRELATION

Overdistention, ischemia, and chemical and mechanical irritation are examples of noxious stimuli resulting in abnormal visceral sensation, which tends to produce dull, achy, **colicky** discomfort.

KEY FACT

Visceral peritoneum has no somatic nerve supply, and pain is poorly localized.

Parietal peritoneum shares somatic innervation with the abdominal wall. Thus, the pain is localized.

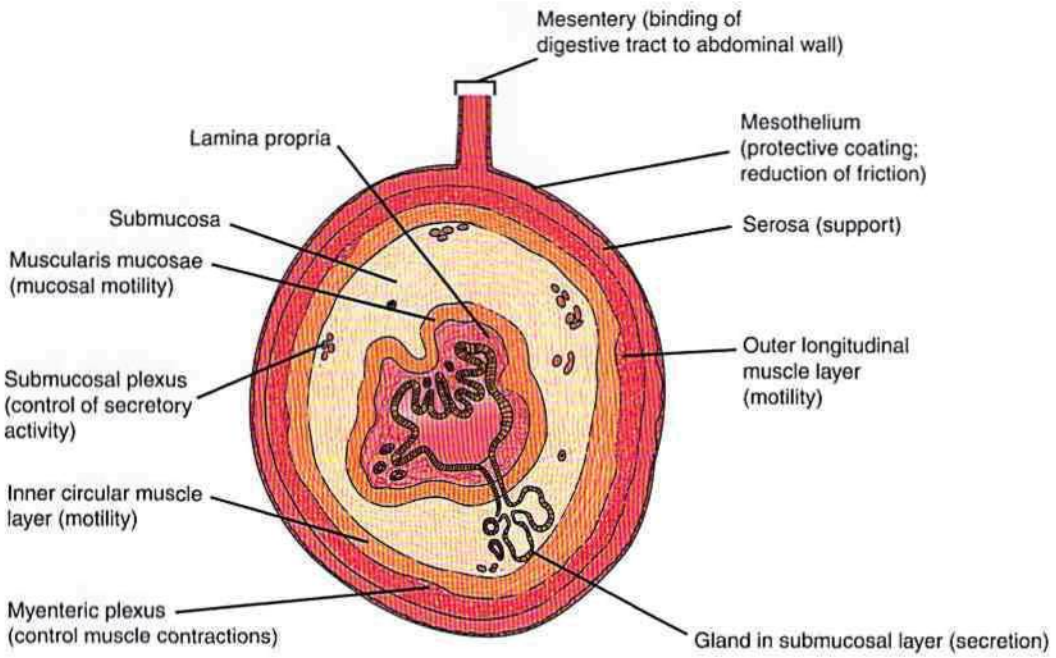


FIGURE 3-11. Cross-section of digestive tract wall.

carry the same types of noxious pain sensations as those overlying the dermatomes. Therefore, parietal pain results in **sharp, localized** pain.

If the pathologic process progresses from the visceral to the parietal region, the referred pain will become localized, corresponding to the dermatome overlying the affected organ.

CLINICAL CORRELATION

Appendicitis begins as **dull, aching, cramping** (visceral) periumbilical pain (approximately in the T10 germatome).

Once the appendiceal inflammation becomes transmural, the parietal peritoneum becomes inflamed, resulting in **sharp pain localized** in the area directly over the appendix (**McBurney's point**).

Referred Pain

Many organs have an embryonic origination in one location of the body and then **migrate** to another area, pulling their vascular and nervous supply with them. Thus, **visceral pain** is often **referred** to sites far removed from the location of that organ (indicating the site of embryonal origin of their respective innervation).

KEY FACT

Visceral sensations from the gut are vaguely localized to the median plane, regardless of the location of the viscus.

Example: The embryologic origin of the diaphragm and its nerves is in the neck. When the diaphragm or the surrounding abdominal structures are inflamed and cause diaphragmatic irritation (i.e., cholecystitis, ruptured spleen), the patient will often feel pain in the shoulder because the corresponding dermatome shares a C3–C4 nerve root with the phrenic nerve. This phenomenon is known as **referred pain.**

The same concept holds true for other abdominal and thoracic organs (see Figure 3-12).

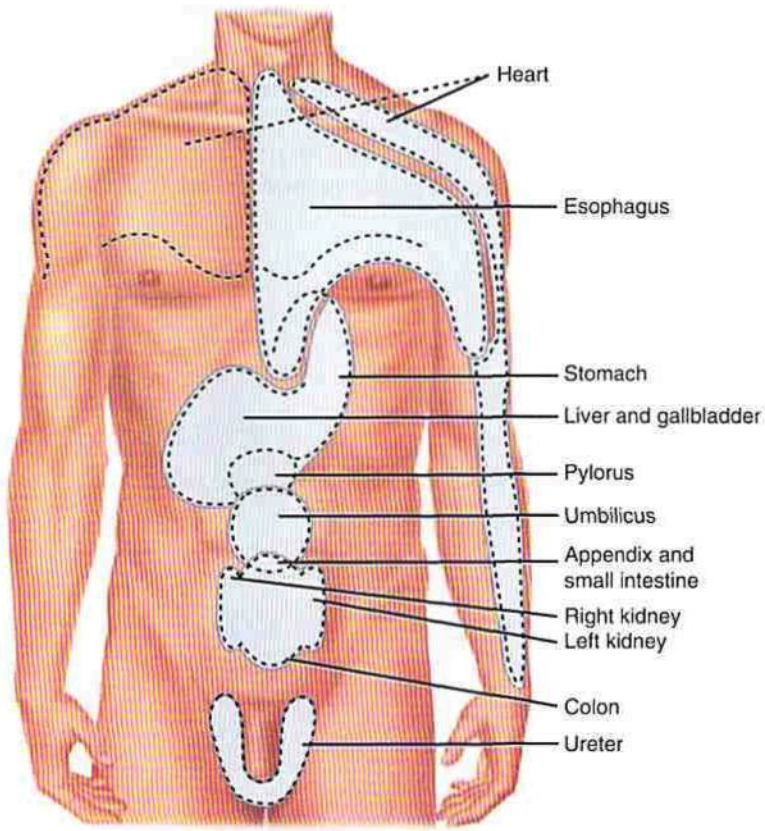


FIGURE 3-12. Location of pain referred from major abdominal and thoracic organs.

ANATOMY AND HISTOLOGY OF THE GI ORGANS

The GI tract is arranged in continuous linear fashion, as a hollow muscular tube, and for the most part exhibits the same wall structure throughout.

In addition to the GI tract (mouth, esophagus, stomach, small and large intestine), multiple accessory organs (salivary glands, liver, gallbladder, and pancreas) have important secretory and metabolic functions.

The general organization of the digestive tract wall, from the lumen outward (see Figure 3-11), is as follows:

The **innermost layer** is the **mucosa,** which consists of an epithelium, lamina propria, and muscularis mucosae.
The **submucosa** consists of fibrous connective tissue and also contains **Meissner's nerve plexus.**
The **muscularis externa** contains three layers of smooth muscle (providing GI motility):
- Circular layer.
- Longitudinal layer: The outermost muscular portion that contains **Auerbach's myenteric plexus.**

The serosa is the outermost layer. Serosa is absent in the esophagus.

Stomach

- **Proximal boundary:** The gastroesophageal junction at the level of T10.
- **Distal boundary:** Ends with the **pyloric sphincter** at the entrance to the duodenum located at L1.
- The inferior and larger curve of the stomach is called the **greater curvature.**
- The smaller curve on the superior aspect of the stomach is known as the **lesser curvature.**

Histologic and Functional Characteristics

- **Mucosa:** Simple glands; secrete mucus and bicarbonate throughout the stomach.
- **Cardia:** Distal to the **lower esophageal sphincter (LES);** does not secrete acid.
- The body (**corpus**): Reservoir and a major site of gastric digestion. Gastric glands in the corpus contain:
  - Parietal cells, which secrete hydrochloric acid.
  - Chief cells, which secrete pepsinogen and intrinsic factor (IF).
- **Pyloric antrum:** Distal region of the stomach that is highly muscular, grinds food, and regulates gastric emptying.
  - **G cells** secrete the hormone **gastrin.**

Small Intestine

Approximately 5-m long, the small intestine is divided into three regions: the duodenum, jejunum, and ileum.

The **duodenum** is mostly retroperitoneal, begins at the gastroduodenal junction at the pyloric sphincter, and is divided into four parts:

- **Superior (first portion):** Marked by the prepyloric vein, is attached to a mobile mesentery, and is located near the common bile duct and the gastroduodenal artery.

KEY FACT

The superior (first) portion of the duodenum is the most common site of duodenal ulcers.

KEY FACT

The horizontal portion of the duodenum is the most common site of traumatic duodenal injuries (crushed against the L3 vertebra).

- **Descending (second portion):** Fixed retroperitoneal location; receives both the common bile duct and the main pancreatic duct through the hepatopancreatic (Vater's) ampulla.
- **Horizontal (third portion):** Fixed retroperitoneal location at the level of L3.
- **Ascending (fourth portion):** Meets the jejunum at the duodenojejunal flexure.

Following the duodenum, the small intestine is mobile and suspended in the peritoneal cavity by mesentery.

The **jejunum** accounts for the proximal three-fifths of the small intestine. The **Ileum** represents the remaining distal two-fifths, **ending** at the **ileocecal valve,** which marks the start of the large intestine.

Histologic and Functional Characteristics

- **Intestinal villi:** Intraluminal projections of the mucosa ~ 1 mm in height, each containing a single terminal branch of the arterial, venous, and lymphatic trees.
- **Enterocytes:** Surface epithelial cells responsible for absorption. Under electron microscopy, numerous microvilli are noted on each enterocyte, further increasing the absorptive surface of the intestine. They make up the **brush border** facing the intestinal lumen.
- **Crypts of Lieberkühn:** Spaces between intestinal villi responsible for cell proliferation (putative multipotential stem cells in the crypts are thought to serve as progenitor cells of the four major cell types contained within the villi: enterocytes, goblet cells, enteroendocrine cells, and Paneth cells).
- **Goblet cells** secrete mucus into the GI lumen.
- **Enteroendocrine cells** secrete hormones into the bloodstream.
- **Paneth cells** produce antimicrobial peptides and growth factors.

The average life span of intestinal cells is 4–6 days.

Large Intestine

The **colon** is divided into several anatomic segments: the cecum, ascending, transverse, descending, and sigmoid colon. Overall length averages 1.5–1.8 m.

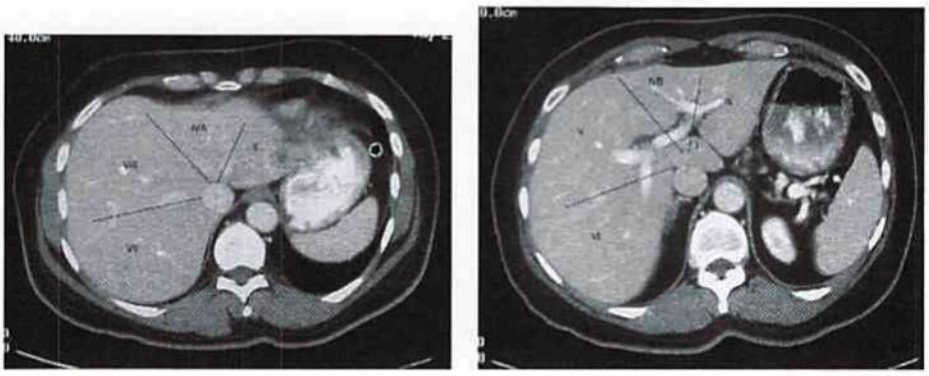
- In contrast to the small intestine, the colon has no villi and only a few folds.
- It contains goblet, endocrine, and absorptive cells.
- Its muscle layer has three longitudinal bands of smooth muscle (tenia coli) and typical haustrations (sacculated wall).

Liver

A large, mostly intraperitoneal organ, positioned just inferior to the diaphragm in the RUQ of the abdomen, typically spanning from the fifth intercostal space in the midclavicular line to the right costal margin.

- On physical exam, the size of the liver can be determined by percussion dullness; usually it is not palpable below the costal margin.

There are two methods (each carrying its own significance) by which to divide the liver.



A B

FIGURE 3-13. Segmental anatomy of the liver by CT scan. (A) The planes of the hepatic veins are demonstrated. These liver segments are cephalad to the portal vein bifurcation. (B) The transverse plane of the portal bifurcation; the noted segments begin here and are caudal to the portal vein bifurcation. (Reproduced, with permission, from Brunicardi FC, Andersen DK, Billiar TR, et al., *Schwartz's Principles of Surgery*, 8th ed, New York: McGraw-Hill, 2005: 1143.)

Anatomically, the liver is divided into **four lobes**: right, left, caudate, and quadrate. The **right and left lobes** are divided by the **falciform ligament,** making the right lobe significantly larger than the left.

Functionally, and based on the blood supply (see Figure 3-13), the liver is divided into eight segments (numbered I–VIII). This division is significant for surgeons as liver resections are done based on this segmental division.

Histologic and Functional Characteristics

- **Hepatocytes** are polygonal epithelial cells arranged in long plates 1–2 cells thick, giving the histologic specimen a very uniform appearance.
- **Liver sinusoids** course between these plates of hepatocytes. They are composed of fenestrated endothelial cells and are in free communication with each other throughout the liver.
- The **liver lobule** (see Figure 3-14) is an anatomic and functional structure created by the radial arrangement of plates of hepatocytes and the intervening sinusoids around the central vein.

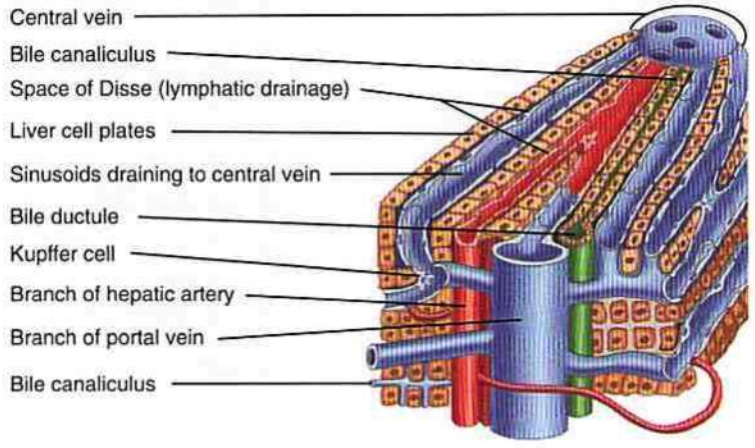


FIGURE 3-14. Detailed structure of the liver lobule. (Modified, with permission, from Chandrasoma P, Taylor CE, *Concise Pathology*, 3rd ed. Originally published by Appleton & Lange. Copyright © 1998 by The McGraw-Hill Companies Inc.)

- Between the endothelial cells of the sinusoids and the hepatocytes themselves is the **space of Disse.**
- **Kupffer cells** are macrophages that are specific to the liver and reside in the liver sinusoids.
- The **lobules of the liver** are hexagonal in shape and separated by connective tissue. Traveling within this connective tissue in between the lobules are the **portal triads: branches of the hepatic artery, portal vein, and bile duct.**

CLINICAL CORRELATION

The dual arterial/venous blood supply is unique to the liver and often prevents ischemia following occlusion or ligation of the hepatic artery.

The liver has a dual blood supply, with 80% of the blood coming from the portal vein and the other 20% from the hepatic artery.

- The **portal venous blood** comes from the venous drainage of the GI tract; it is therefore rich in nutrients but lacks oxygen. This blood allows the liver to perform its metabolic functions.
- The **arterial supply** to the liver is responsible for oxygenating the hepatocytes and supporting liver cells.

Gallbladder

The gallbladder is a small sac-like structure located on the inferior surface of the liver. It is **divided into the fundus, body, and neck;** it then narrows into the **cystic duct,** which is the structure that drains the gallbladder (see Figure 3-15).

- The cystic duct then joins with the **common hepatic duct** to form the common bile duct.
- The **common bile duct** descends and finally joins with the pancreatic duct at the **ampulla of Vater** to empty into the second portion of the duodenum.

Histologically, the mucosa of the gallbladder is composed of simple columnar epithelium in which all of the cells are virtually identical.

- It is folded when the gallbladder is empty, which can cause it to resemble intestinal epithelium; the gallbladder is distinguished by its lack of goblet cells and crypts.

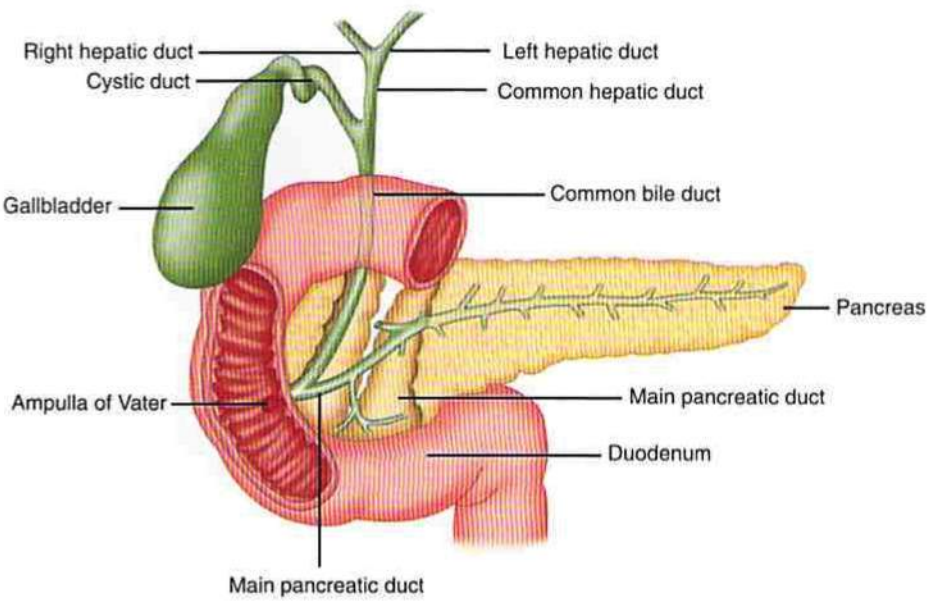


FIGURE 3-15. The gallbladder and its surrounding structures.

Physiology

HYPOTHALAMUS

The hypothalamus controls the body's sense of hunger and fullness.

- **Lateral hypothalamic area (LHA):** Sensation of hunger (i.e., stimulates feeding).
- **Ventromedial nucleus of the hypothalamus (VNH):** Sensation of fullness (i.e., tells the animal to stop feeding).

KEY FACT

Lesions of the:
- LHA can cause anorexia.
- VNH can cause obesity.

KEY FACT

Leptin is a protein hormone released from adipocytes. It acts on many parts of the hypothalamus, especially the arcuate and paraventricular nuclei. Leptin decreases appetite and increases metabolism.

MOUTH

The mouth is the first site of digestion. It is the site of mechanical breakdown of the food by mastication (chewing).

- The **chewing reflex** causes the up-and-down movement of the lower jaw.
- Most of the **muscles of mastication** are **innervated** by the **trigeminal nerve (CN V).**

Salivary Secretions

The salivary glands (see Figure 3-16) produce approximately 1.5 L of saliva each day. Saliva helps moisten and digest food, while protecting the oral cavity from bacteria.

- **Major salivary glands** include the parotid, submandibular (submaxillary), and sublingual glands.
- **Minor salivary glands** include a group of tiny glands located in the buccal mucosal area.
- **Parasympathetic stimulation:** An **increase** in the secretion of watery saliva is mediated by **CN VII** (facial nerve) and **CN IX** (glossopharyngeal nerve) from the superior and inferior salivatory nuclei in the brain stem via **muscarinic receptors.**
- **Sympathetic stimulation** is mediated via **β-adrenergic receptors,** and causes an increase in secretion of **viscous** saliva (via T1–T3 nerves of the superior cervical ganglion).

KEY FACT

Peptide YY is produced by the small intestine and colon and reduces appetite in response to eating.

KEY FACT

Anticholinergic drugs, such as atropine, cause dry mouth.

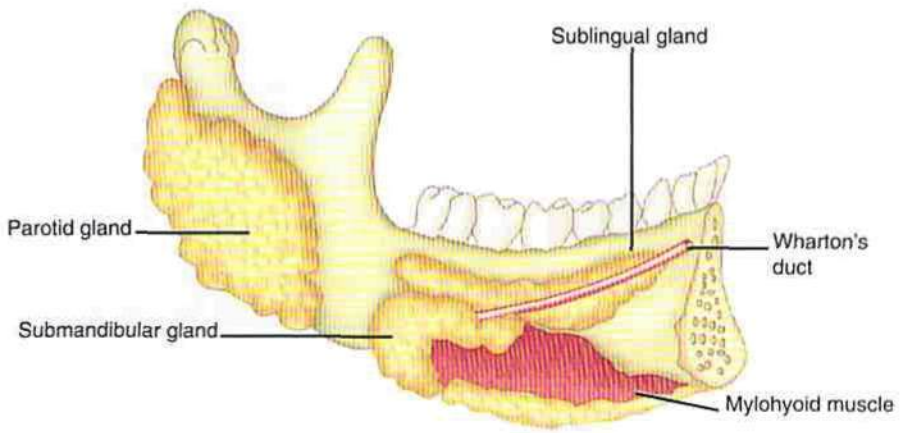


FIGURE 3-16. The major salivary glands. (Image courtesy of Armed Forces Institute of Pathology via PEIR Library [http://peir.net].)

The two major types of salivary protein secretions are serous (α-amylase; primarily parotid gland) and mucous (mucin). The submandibular and sublingual glands are a mixture of serous and mucous glands.

Composition of Saliva

- **Enzymes:**
  - **α-Amylase (ptyalin):** Begins digestion of carbohydrates, particularly starches, by hydrolyzing α-1,4 bonds. It is **inactivated** by the **low pH** of the **stomach.**
  - **Lingual lipase:** Begins digestion of lipids; breaks down triglycerides into fatty acids and monoglycerides. It is capable of continued digestion within the stomach. **In contrast to pancreatic lipase,** it can cleave fatty acids from all three positions on a triglyceride.
- **Ions:**
  - High in bicarbonate and potassium.
  - Low in sodium and chlorine.
- **Tonicity:**
  - In low flow rate states, saliva is hypotonic relative to plasma, with high Na+ and Cl– and low K+.
  - In high flow rate states, saliva is closer to isotonic (relative to plasma), with low Na+ and Cl– and high K+.
- The **pH** is between 6 and 7.
- **Antibacterial actions:** The flow of saliva and enzymes and antibodies help to fight dental caries:
  - Lysozyme attacks bacteria and digests food particles.
  - Lactoferrin.
  - Thiocyanate ions enter bacteria and become bactericidal.
  - Antibodies (IgA).
  - Defensins.

KEY FACT

Aldosterone causes an increase in the secretion of K^+ and reabsorption of Na^+ and Cl^-, similar to its actions in the renal distal tubule.

Swallowing (Deglutition)

Deglutition is a process regulated by the **swallowing reflex,** which is **coordinated in the medulla.** Simply stated, swallowing is propulsion of the bolus through the pharynx while respiration is temporarily blocked. There are **three stages** of swallowing: voluntary, pharyngeal, and esophageal.

- **Voluntary stage:** The bolus is pushed to the posterior of the pharynx by the tongue.
- **Pharyngeal phase:** Initiated through the epithelial swallowing receptor reflex.
- **Esophageal phase:** See the esophagus section for an explanation.

The **pharyngeal phase (epithelial swallowing receptor reflex)** is carried out through the following steps:

- **Upward movement of the soft palate** to prevent reflux of food into the nasal cavities.
- **Constriction of the palatopharyngeal folds,** which creates a small passageway that permits only properly masticated food to pass into the posterior pharynx.
- **Closure of the glottis** to prevent passage of food into the trachea.
- **Tightening of the vocal cords** and upward movement of larynx, causing the epiglottis to swing backward over the opening of the larynx.
- The **upper esophageal sphincter (UES) relaxes in < 1 second.**

ESOPHAGUS

The esophagus is a muscular tube lined with **nonkeratinized stratified squamous epithelium.** It connects the pharynx through the UES to the stomach via the LES.

- **Upper esophagus:** Mostly skeletal muscle; primarily controlled by the nucleus ambiguus.
- **Lower esophagus:** Predominantly smooth muscle; controlled by the dorsal nucleus of the vagus nerve.

The esophagus quickly propels food toward the stomach via **peristaltic contractions,** and is controlled by:

- The **extrinsic nervous system:** The sympathetics and parasympathetics of the CNS.
- The **intrinsic nervous system** (enteric nervous system): Myenteric **(Auerbach's)** plexus, which promotes motility of smooth muscle, and the submucosal **(Meissner's) plexus,** which controls secretion and blood flow.
  - The enteric nervous system uses **ACh, dopamine,** and **serotonin** as neurotransmitters.

Under physiologic conditions, the average resting esophageal pressures **(if the pharynx is at 0 mmHg)** are:

UES = +100 mmHg
Esophagus = –5 mmHg
LES = +20 mmHg
Stomach = +5 mmHg

Swallowing

The **esophageal phase** of deglutition involves movement of food toward the stomach, causing **relaxation of the LES** as a result of **vagal stimulation.**

- **Primary peristalsis** is a continuous peristaltic wave. Food movement is accelerated by gravity.
- **Secondary peristalsis** is a reflexive reaction. Distention of the esophagus triggers a peristaltic contraction that clears the esophagus of remaining food.
- As food passes down the esophagus it triggers the proximal region of the stomach to relax, a phenomenon known as **receptive relaxation.**

Increased pressure applied to the UES induces emesis (vomiting), which can be caused by:

- Gastric overdistention.
- Oropharyngeal stimulus.
- Chemoreceptor trigger of the area postrema of the medulla.
- Vestibular stimulus.

STOMACH

The food bolus undergoes further mechanical and chemical breakdown in the stomach. These processes are enabled by several substances secreted by the stomach.

- Once the bolus is propelled through the pyloric sphincter into the duodenum, it is known as **chyme.**

FLASH FORWARD

Chronic gastroesophageal reflux disease (GERD) can lead to **Barrett's esophagus,** which is metaplasia of stratified squamous epithelium into the columnar epithelium.

KEY FACT

Intraesophageal pressure equals thoracic pressure; both are lower than the atmospheric pressure.

CLINICAL CORRELATION

Poor tone of the **LES** can lead to **GERD.**

CLINICAL CORRELATION

Damage to the myenteric plexus in the lower two-thirds of the esophagus causes **achalasia** (failure of the LES to relax; see Figure 3-17).

CLINICAL CORRELATION

Over time, the esophagus dilates and barium swallow shows a classic **"bird's-beak" esophagus.**

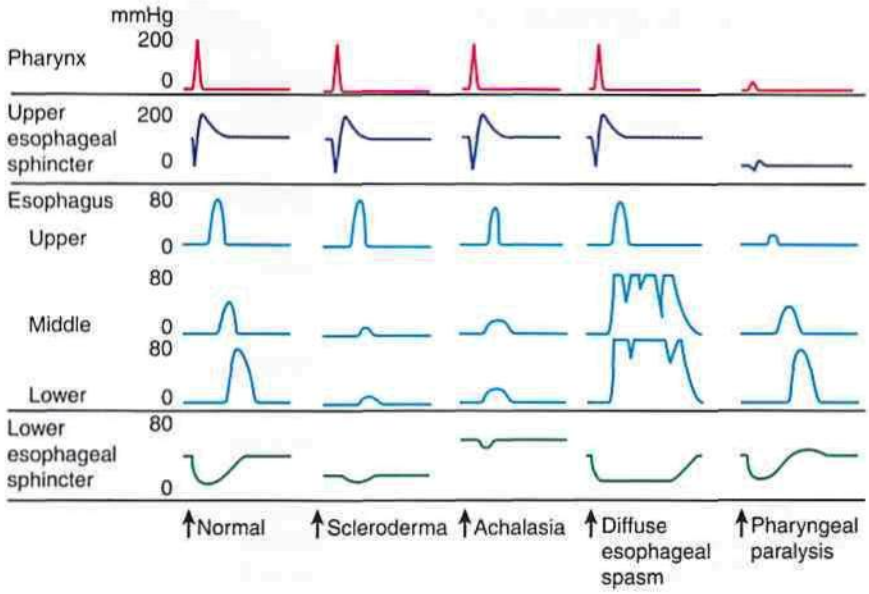


FIGURE 3-17. Motility patterns in selected esophageal and pharyngeal disorders. (Modified, with permission, from Kasper DL, Braunwald E, Fauci AS, eds, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 1741.)

FLASH BACK

Pyloric stenosis is a congenital condition in which the muscle of the pyloric sphincter is too hypertrophied to allow the passage of chime, resulting in projectile vomiting. The classic physical finding is an olive-shaped mass on abdominal exam.

The stomach's baseline rate of contractions (3–5 contraction waves every minute) is known as the **basal electric rhythm**.

- **Parasympathetic** stimulation of the vagus nerve **increases** stomach contractions.
- **Sympathetic** stimulation of the celiac plexus **decreases** stomach contractions.
- **Migrating motility complex (MMC):** Contractions of the stomach and small intestine during fasting conditions. These contractions occur in a cyclic motor pattern and prevent bacterial overgrowth (**housekeeping**).
  - They **repeat every 90–120 minutes** and are mediated by **motilin.**

The stomach's main motor functions include storage, mixing, emptying, and hunger contractions.

- Food is **stored** for about 45 minutes and undergoes mixing before it is squeezed out via the pyloric sphincter.
  - **Retropulsion:** Phasic type of contraction during which the pyloric sphincter narrows. Allows for more efficient **mixing** of the bolus in the stomach.
- **Emptying** of the stomach is enabled by an intense contraction, which pushes the food through the pyloric sphincter.

The rate of stomach emptying is controlled by the content of food.

- Hypotonic or hypertonic food delays gastric emptying.
- The presence of lipids and partially digested proteins in the food stimulates the release of cholecystokinin (CCK), which decreases gastric motility, thus delaying gastric emptying.
- Increase of H^+ in the duodenum inhibits gastric emptying.

Regulation of Gastric Secretions

Gastric secretion occurs in three interrelated stages: **cephalic, gastric,** and **intestinal phases.**

- **Cephalic phase:** Parasympathetic stimulation from the appetite centers of the hypothalamus and/or amygdala to the stomach produces salivary and gastric secretions due to the sight, smell, thought, or other neurologic stimuli of food.
- **Gastric phase:** Stimulated by long vagovagal and enteric reflexes that increase acid production through the **release of gastrin** due to distention of the stomach.
- **Intestinal phase:** Further release of gastrin from the duodenum as a result of the presence of protein in the upper portion of the small intestine.

The **presence of chyme** in the intestines stimulates gastric secretion in the intestinal phase. However, it also **paradoxically inhibits gastric secretion** via the **reverse enterogastric reflex,** as well as through the release of several hormones, including secretin, gastric inhibitory peptide, vasoactive intestinal peptide (VIP), and somatostatin.

The inhibition of gastric secretions helps regulate the amount of chyme entering the duodenum.

The secretory products of the stomach are depicted in Table 3-6.

Mechanism of Hydrochloric Acid Secretion

HCl is secreted by the parietal cells in the stomach and regulated by the **proton pumps,** which exchange a proton for potassium. Chlorine follows the electrical gradient (see Figure 3-18).

- **Mechanism** of gastric HCl secretion in parietal cells:
  - $CO_2 + H_2O \rightarrow H^+ + HCO_3^-$ via the action of carbonic anhydrase.
  - H^+-K^+ pump secretes H^+ into the stomach lumen.
  - HCO_3^- and Cl^- are exchanged through the bloodstream, and Cl^- follows H^+ into the stomach lumen.

KEY FACT

Pepsinogen is a zymogen precursor of pepsin activated by:
- Acid
- Pepsin (autocatalysis)

KEY FACT

"Alkaline tide" is the name for the phenomenon seen when the pH of the blood increases, and that in turn makes the urine more alkaline after a large meal, due to an increase in HCO_3^-.

FLASH FORWARD

The proton pump inhibiters (PPIs, i.e., omeprazole) function to inhibit gastric acid secretion.
H_2-receptor antagonists, such as cimetidine decrease the secretion of histamine.

TABLE 3-6. Gastric Secretions

Product	Source	Location	Action	Regulation Stimulus	Regulation Inhibition
Gastric acid (HCl)	Parietal (oxyntic) cells	Body, fundus	▪ Aids in digestion. ▪ Activates pepsin from pepsinogen. ▪ Kills pathogens.	Gastrin, ACh (vagus), histamine.	Low pH, prostaglandins, GIP secretion (negative feedback), somatostatin.
Intinsic Factor (IF)	Parietal (oxyntic) cells	Body, fundus	▪ Binds to vitamin B_{12}, leading to its uptake in the ileum.	Gastrin, ACh (vagus), histamine.	Low pH, prostaglandins, GIP secretion (negative feedback), somatostatin.
Pepsinogen	Chief cells	Body, fundus	▪ Precursor for pepsin ▪ Digests protein at a pH between 1.0 and 3.0.	Gastrin, ACh (vagus), histamine.	Somatostatin.
Mucus	Mucous cells	Entire stomach	▪ Protects mucosa from the acidic environment and pepsin.	Contains Acetylcholine (vagus).	
HCO_3^-	Mucous cells	Entire stomach	▪ Neutralizes acid.	Secretin.	

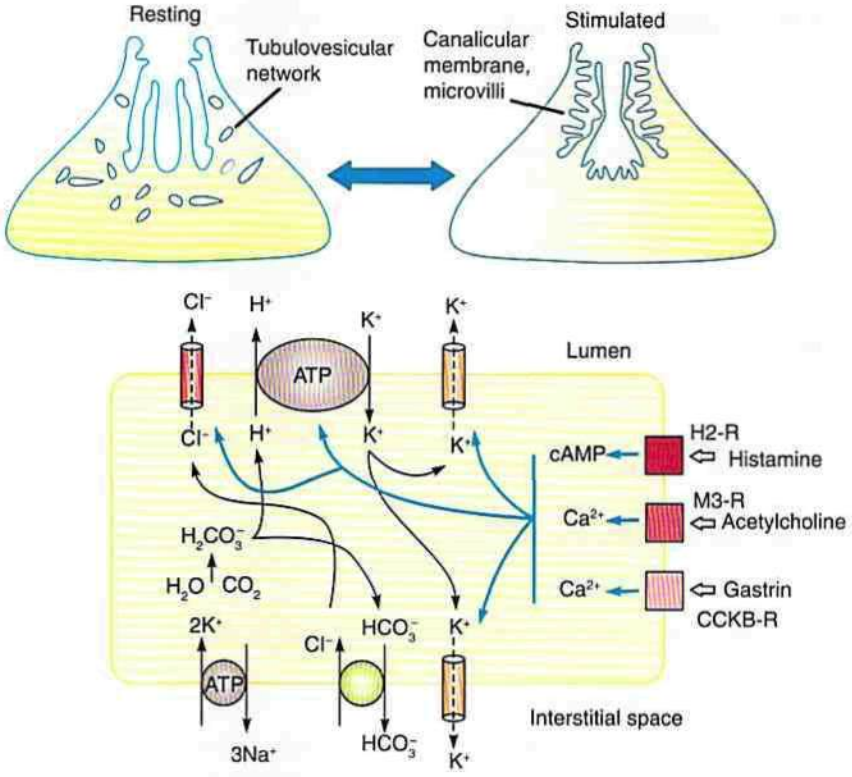


FIGURE 3-18. Acid secretion by parietal cells. Top: Upon stimulation, the tubulovesicular network in the parietal cell fuses to form an extensive canalicular membrane with microvilli, which increases the surface area. Bottom: The mechanisms of HCl secretion by parietal cells, stimulated by histamine, ACh, and gastrin, are demonstrated. M3-R, muscarinic 3-receptor; H2-R, histamine 2-receptor; CCKB-R, CCK B receptor. (Modified, with permission, from McPhee SJ, Ganong WF, *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 5th ed, New York: McGraw-Hill, 2006: 353.)

CLINICAL CORRELATION

Zollinger-Ellison's syndrome (gastrinoma) is seen when an abnormally large amount of gastrin is secreted by the non-β-cell tumors of the pancreas, leading to multiple gastric and intestinal ulcers.

Absorption

The stomach is capable of absorbing alcohol and lipid-soluble drugs, such as aspirin.

Hormones and Peptides

Hormones and peptides regulate the digestion and absorption of food throughout the GI tract. They are released from endocrine cells found in the GI mucosa and enter the portal venous circulation.

The following GI hormones are found in the stomach:

KEY FACT

Phe and Trp are strong stimulators of gastrin.

KEY FACT

GRP and VIP are found in the suprachiasmatic nuclei of the hypothalamus and may play a part in mammalian circadian rhythm.

Gastrin

- **Anatomic significance:** Produced by **G cells** in the antrum of the stomach and duodenum. Its secretion is controlled by several factors:
  - **Stimulated** by stomach distention, amino acids and peptides present in the lumen of the small intestine, and vagal influence.
  - **Inhibited** by an increase in H^+ in the lumen of the stomach.
- **Physiologic action:** Gastrin **stimulates:**
  - **Parietal cells** to increase gastric acid secretion.
  - **Chief cells** to secrete pepsinogen.
  - **Enterochromaffin-like (ECL) cells** (neuroendocrine cells found in the GI mucosa) to secrete histamine.
  - Growth of gastric mucosa (**trophic action**).
  - Gastric motility.

Gastrin-Releasing Peptide (GRP)

Produced by vagal postganglionic nerve endings in response to gastric distention and the cephalic phase of gastric secretions.

- **Stimulates the release of gastrin** from G cells.

KEY FACT

Atropine does not block gastrin secretion because this hormone is mediated by GRP instead of ACh.

SMALL INTESTINE

The main function of the small intestine is digestion and absorption of food and nutrients using digestive enzymes (see Table 3-7). Because digestive enzymes can only interact on the surface of chyme, the surface area of ingested food must be increased. The great length and tubular structure of the intestines, as well as the endothelial brush border, increase the surface area, aiding absorption.

TABLE 3-7. Small Intestinal Secretions

Product	Source	Location	Action	Regulation Stimulus
Cl^-	Crypts of Lieberkühn	Entire small intestine	Makes a watery fluid for easier absorption.	CCK, secretin, enteric nervous reflexes
HCO_3^-	Crypts of Lieberkühn	Entire small intestine	Makes a watery fluid for easier absorption. Helps neutralize gastric acids.	CCK, secretin, enteric nervous reflexes
Peptidases	Brush border enterocytes	Entire small intestine	Hydrolysis of dipeptides and tripeptides into amino acids.	Enteric nervous reflexes
Sucrase	Brush border enterocytes	Entire small intestine	Hydrolysis of sucrose into fructose and glucose.	Enteric nervous reflexes
Maltase	Brush border enterocytes	Entire small intestine	Hydrolysis of maltose into two glucoses.	Enteric nervous reflexes
Isomaltase	Brush border enterocytes	Entire small intestine	Hydrolysis of saccharides not digested earlier.	Enteric nervous reflexes
Lactase	Brush border enterocytes	Entire small intestine	Hydrolysis of lactose into galactose and glucose.	Enteric nervous reflexes
α-Dextrinase	Brush border enterocytes	Entire small intestine	Hydrolysis of terminal α-1,4 bonds, to make glucose.	Enteric nervous reflexes
Intestinal lipase	Brush border enterocytes	Entire small intestine	Breakdown of neutral fats into fatty acids and glycerol.	Enteric nervous reflexes
Heavy alkaline mucus	Brunner's glands	Duodenum	Protects duodenum from the large amount of gastric acid.	Secretin, tactile/irritating, ACh (vagus)
Mucus	Goblet cells	Entire small intestine	Lubricates and protects intestines.	Enteric nervous reflexes

The small intestinal endothelium is constantly turning over with new endothelial cells due to the large amount of wear and tear.

- **Goblet cells** (specialized endothelial cells) aid in the lubrication and transit of chyme through the small intestine by producing mucus (a protective glycoprotein).

KEY FACT

The small intestine does not store food.
Contraction waves: Initiated by ACh and substance P.
Relaxation: Initiated by VIP and nitric oxide.

The **basal electric rhythm** of the **small intestine** is **faster** than that of the **stomach**: 12 waves per minute in the duodenum and 8–9 waves per minute in the ileum.

- Chyme is **mixed** via **segmental** contractions and **propelled forward** with **peristaltic** contractions (which increase with parasympathetic stimulation from the vagus nerve and decrease with sympathetic stimulation from the mesenteric ganglion).
- Fasting MMC occurs every 90 minutes.

Absorption

The primary location for absorption of nutrients is the small intestine. This is due to the specialized surface endothelial villi structures known as the **brush border,** which greatly increases the surface area of the small intestine to more efficiently absorb nutrients. The small intestine absorbs nutrients from the chyme in the stomach.

FLASH BACK

Vibrio cholerae produces the cholera toxin, which causes increased secretion of chlorine, leading to **osmotic diarrhea.**

- **Nonfat, water-soluble** nutrients are absorbed through the small intestine into the portal vein, where they are transported to the liver for storage and processing.
- **Fat-based nutrients** enter into the mesenteric lymphatic system of the intestines and bypass the liver.

Duodenum

This small section of the small intestine is responsible for much of the absorption of nutrients:

KEY FACT

Lactase deficiency is a common cause of osmotic diarrhea and flatus in African American, Mediterranean, and Asian populations.

- **Water** and **ions** such as sodium, chloride, and potassium are absorbed passively with solutes. Sodium can facilitate the absorption of other nutrients through a cotransporter.
- **Glucose** and **galactose** (see Figure 3-19):
  - Compete for absorption in the **luminal side** of the enterocyte via a sodium-dependent cotransporter known as **SGLT1.**
  - A **sodium-potassium pump** on the **basolateral side** maintains the low sodium gradient within the cell.

KEY FACT

Dietary energy from absorbed substances:
- Carbohydrates: 4 Kcal/g
- Proteins: 4 Kcal/g
- Fats: 9 Kcal/g

Glucose and galactose exit the cell **basolaterally** through the **GLUT 2** transporter.

- **Lipids** (see Figure 3-20) are emulsified by bile acids in the small intestine and form micelles due to their hydrophobic nature. **Micelles** transport fatty acids, cholesterol, and monoglycerides to the brush border of the enterocytes. Glycerol is hydrophilic and is not part of the micelle body.
  - **Within the enterocyte,** re-esterification of the fatty acids, monoglycerides, and cholesterol takes place to form triglycerides and cholesterol esters.
  - Triglycerides and cholesterol esters are mixed with apoproteins and form **chylomicrons.**
  - Chylomicrons then enter the lymphatic system and enter the bloodstream via the thoracic duct.
- **Vitamins A, D, E, and K** are fat-soluble vitamins that are absorbed within micelles with fatty acids and cholesterol.

KEY FACT

Only monosaccharides such as glucose, galactose, and fructose can be absorbed.

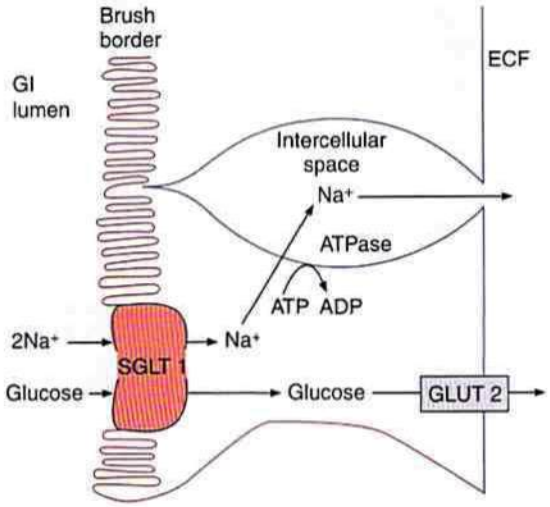


FIGURE 3-19. Mechanism for glucose transport across intestinal epithelium. (Modified, with permission, from Ganong WF, *Review of Medical Physiology*, 22nd ed, New York: McGraw-Hill, 2005: 472.)

CLINICAL CORRELATION

Abetalipoproteinemia is an inability of chylomicrons to leave the enterocyte due to a lack of β-apolipoprotein.

PROXIMAL JEJUNUM

The absorption of glucose, galactose, lipids, and vitamins A, D, E, and K continue in this portion of the small intestine. In the proximal jejunum, the digestion of some additional nutrients begins.

- **Fructose** is absorbed via facilitated diffusion on the luminal surface of the intestines through the GLUT 5 transporter. It is absorbed basolaterally through the GLUT 2 transporter, the same transporter as that for glucose and galactose.

FLASH BACK

Fat-soluble vitamins (**A, D, E, and K**) are lost in **steatorrhea** (fatty stool).

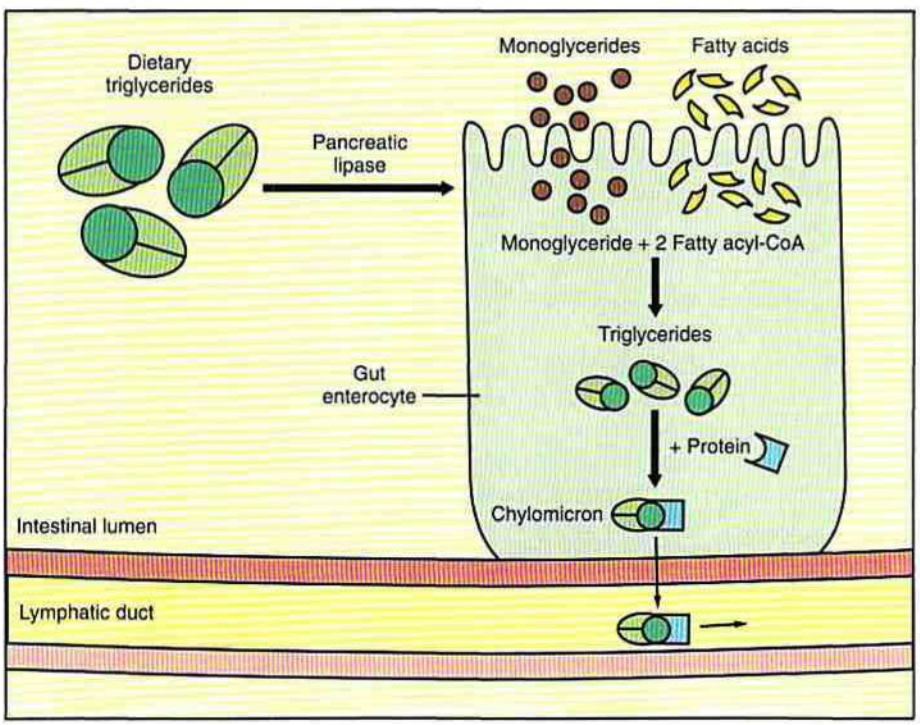


FIGURE 3-20. Mechanism of lipid absorption. (Modified, with permission, from Brunicardi FC, Andersen DK, Billiar TR, et al., *Schwartz's Principles of Surgery*, 8th ed, New York: McGraw-Hill, 2005: 27.)

CLINICAL CORRELATION

Vitamin D deficiency:
In children = Rickets
In adults = Osteomalacia

FLASH BACK

Distinguish marasmus from kwashiorkor:

Marasmus: Small child with "E.T. face" (pinched, no cheeks) who is hungry (begging for food).

- Results from diet deficient in total calories and vitamins (starvation or anorexia nervosa).

Kwashiorkor: Small child with moon face (fat cheeks) and swollen belly who is apathetic.

- Results from protein-deficient **MEAL(L)**s:

Malabsorption
Edema
Anemia
Liver is fatty, dysfunctional
Low serum albumin

KEY FACT

Vitamin B_{12} deficiency can result from a loss of IF, such as in pernicious anemia or following gastrectomy.

CLINICAL CORRELATION

In patients with **cholelithiasis**, pain increases after fatty meals due to increased secretion of CCK, which induces gallbladder contraction.

- **Protein** can be absorbed as tripeptides, dipeptides, and amino acids. Most amino acids have specific sodium-dependent cotransporters. Tripeptides and dipeptides are absorbed via a proton-dependent cotransporter.

Terminal Jejunum

Continues to absorb glucose, galactose, fructose, lipids, protein, and vitamins A, D, E, and K. The digestion of some additional nutrients begins in the terminal jejunum:

- **Water-soluble vitamins** are absorbed via specific sodium-dependent cotransporters.

Ileum

The absorption of protein continues. It can act as a reserve for additional nutrients that have not yet been absorbed. Some additional nutrients begin to be absorbed in the ileum:

- **Vitamin B_{12}** (bound to IF) is absorbed via specific receptors in the ileum.

Hormones and Peptides

GI hormones and peptides found in the small intestine include:

Gastrin

See stomach section.

Cholecystokinin

- **Anatomic significance:** Produced by **I cells** in the duodenum and jejunum.
  - **Release is stimulated** by fatty acids and amino acids present in the small intestine.
  - **Release is inhibited** by secretin and low stomach pH.
- Physiologic action:
  - **Stimulates** pancreatic enzyme secretion (amylase, lipases, and proteases), gallbladder contraction, relaxation of the sphincter of Oddi, and growth of exocrine pancreas and gallbladder cells.
  - **Inhibits** emptying of the stomach.

Secretin

- **Anatomic significance:** Produced by **S cells** in the **crypts of Lieberkühn** of the duodenum.
  - **Release is stimulated** by decreased pH in the stomach and the presence of fatty acids in the duodenum.
- **Physiologic action:**
  - **Stimulates** pancreatic bicarbonate secretion (neutralizes gastric acid to allow pancreatic enzymes to function correctly), production of bile by the liver, and growth of exocrine pancreas cells.
  - **Inhibits** gastric acid secretion.

Somatostatin

- **Anatomic significance:** Produced by **D cells** in the duodenum, **delta cells** of the pancreatic islets, and **GI mucosa** cells.
  - Release **stimulated** by gastric acid.
  - Release **inhibited** by vagal stimulation.

- **Physiologic action:**
  - **Inhibits** gastric acid and pepsinogen secretion, pancreatic and small intestine fluid secretion, gallbladder contraction, and insulin and glucagon release.

Gastric Inhibitory Peptide

- **Anatomic significance:** Produced by **K cells** of the duodenum and jejunum.
  - Release **stimulated** by amino acids, fatty acids, and oral glucose.
- **Physiologic action:**
  - **Stimulates** release of insulin.
  - **Inhibits** gastric H^+ secretion.

Pancreatic Polypeptide

See pancreas section.

Enteroglucagon

- **Anatomic significance:** Produced by **L cells** of the small intestine.
- **Physiologic action:**
  - **Stimulates** release of insulin.
  - **Inhibits** gastric and pancreatic secretions.

Motilin

- **Anatomic significance:** Produced by **enterochromaffin cells** in the duodenum and jejunum.
  - Release stimulated by the absence of food for > 2 hours.
- **Physiologic action: Stimulates** MMC in the stomach and small intestines as well as the production of pepsin.

Histamine

- **Anatomic significance:** Secreted by ECL cells.
  - Release stimulated by gastrin and ACh.
- **Physiologic action: Stimulates** the secretion of gastric acid.

Vasoactive Intestinal Peptide

- **Anatomic significance:** Produced by enteric neurons and the pancreas.
  - Release **stimulated** by intestinal distention and vagal activation.
- **Physiologic action: Stimulates** receptive relaxation of the stomach and relaxation of intestinal smooth muscle, intestinal secretion of water and electrolytes, and increased release of pancreatic bicarbonate.

COLON

The main function of the colon is the reabsorption of electrolytes and water as well as short-term storage of undigested material (feces), followed by its excretion. The colon is larger in diameter than the small intestine and is inhabited by normal bacterial flora.

- These bacteria synthesize **vitamin K**, B-complex vitamins, folic acid, and **short-chain fatty acids** (a preferred source of nutrition by colonocytes), and metabolize nitrogen.
- The colon has **slow waves** that slowly mix the feces, allowing fluid reabsorption in the ascending colon with **haustrations** (segmental contrac-

KEY FACT

Somatostatin is an inhibitory and anti-growth hormone.

KEY FACT

Oral glucose results in a faster release of insulin than the equivalent amount of glucose given IV because of increased release of gastric inhibitory peptide due to the oral glucose stimulus.

KEY FACT

VIPoma is a tumor usually found in the pancreas that produces an excess of VIP, causing chronic diarrhea.

KEY FACT

Bacterial lipases hydrolyze fatty acids into hydroxyl fatty acids, such as oleic acid, which stimulates fluid secretion within the colon.

KEY FACT

Undigested material travels from the ileocecal valve to the anal sphincter.

KEY FACT

There is no MMC in the colon.

KEY FACT

The colon can secrete excess potassium in diarrhea, resulting in hypokalemia.

tions), which take about 8–15 hours and cause a net movement of feces to the transverse colon, where transit speed tends to increase.

- **Large contractions** of the colon (**mass movements**) prepare stool to be eliminated.
- **Contractions increase** with parasympathetic stimulation of the vagus and sacral nerves and **decrease** with sympathetic stimulation from the mesenteric ganglion.
- When the stomach is full, it can cause a reflex known as the **gastrocolic reflex,** which **increases** the frequency of **mass movements.**

The colon is capable of secreting **potassium** and bicarbonate.

The colon is the most efficient absorber of water via actively transported sodium. It can also absorb chloride, potassium, and short-chain fatty acids.

EXOCRINE PANCREAS

The pancreas acts as an **exocrine gland** (via acini and ducts) and **endocrine gland** (via islets of Langerhans). The exocrine portion of the pancreas has a major role in digestion. The serous acini of the pancreas synthesize and store a large number of inactive enzymes known as zymogens, keeping them ready to be released into the duodenum when necessary.

Hormones and Peptides

GI hormones found in the pancreas include:

- **Somatostatin:** See small intestine section.
- **Pancreatic peptide:** Produced by **F cells (PP cells)** of the pancreas and small intestines, its release is stimulated by protein, fat, and glucose in the intestinal lumen.
  - Inhibits the release of pancreatic secretions.
- **VIP:** See the small intestine section.

CLINICAL CORRELATION

Pancreatitis results from overwhelmingly activated zymogens and proenzymes within the pancreas, leading to self-digestion. **Cystic fibrosis** (CF) is a disorder of the CF transmembrane conductance regulator protein that results in a defect of the Cl^- channels. CF is associated with a deficiency of pancreatic enzymes.

Pancreatic Enzymes

Pancreatic secretions (see Table 3-8) contain enzymes that can digest carbohydrates, protein, fats, and nucleic acids. They also contain a large amount of bicarbonate to neutralize gastric acid within the duodenum.

- The **release of pancreatic secretions** is controlled by CCK, secretin, and ACh from the vagus nerve.

Pancreatic enzymes are produced in an inactive form known as **zymogen** (proenzyme) by the exocrine serous glands of the pancreas.

- Once the inactive and active enzymes are excreted out the pancreatic duct via the papilla of Vater, **trypsinogen is activated** by the duodenal brush border enzyme **enteokinase** to become **trypsin.**
- Trypsin can activate the remaining zymogens and proenzymes into their active form.
- The pancreas produces enzyme inhibitors to inactivate trace amounts of active enzymes within the pancreatic parenchyma.

KEY FACT

Pancreatic deficiency can lead to malabsorption, steatorrhea, and fat-soluble vitamin deficiency.

TABLE 3-8. Pancreatic Enzymes

Enzyme	Zymogen/Proenzyme	Enzyme Class	Catalyzing Activity
Pancreatic amylase	None (secreted as active form)	Polysaccharidase	▪ Hydrolysis of starch to oligosaccharides and disaccharides. ▪ Hydrolysis of glycogen. ▪ Does **not** hydrolyze cellulose.
Trypsin	Trypsinogen	Protease	▪ Activates other pancreatic zymogens. ▪ Hydrolysis of proteins into peptides.
Chymotrypsin	Chymotrypsinogen	Protease	▪ Hydrolysis of proteins into peptides.
Carboxypeptidase	Procarboxypeptidase	Protease	▪ Hydrolysis of peptides into amino acids.
Elastase	Proelastase	Protease	▪ Hydrolysis of elastin from collagen fibers.
Pancreatic lipase	None (secreted as active form)	Lipase	▪ Hydrolysis of neutral fats into fatty acids and monoglycerides.
Cholesterol esterase	Proesterase	Lipase	▪ Hydrolysis of cholesterol esters into cholesterol and fatty acids.
Phospholipase	Prophospholipase	Lipase	▪ Hydrolysis of phospholipids into fatty acids, glycerol, and phosphate.
Ribonuclease	None (secreted as active form)	Nuclease	▪ Hydrolysis of RNA into ribonucleotides.
Deoxyribonuclease	Prodeoxyribonuclease	Nuclease	▪ Hydrolysis of DNA into deoxyribonucleotides.

LIVER AND GALLBLADDER

Liver Overview

The liver has a multifactorial role in human physiology.

- **Aids digestion:** Synthesis of bile acids. Most of the **bile** produced by the liver is **recycled;** once absorbed through the ileum, it travels up the portal vein into the liver via **enterohepatic circulation.**
- Serves as the **first site of metabolism** of ingested food absorbed from the small intestine.
- Maintains the body's blood chemistry. The liver is the site of many key biochemical processes, such as gluconeogenesis and glycolysis.
- Stores excess sugar in the form of glycogen and triglycerides. Breaks down glycogen and produces glucose from triglycerides and amino acids when blood glucose levels are low.

Gallbladder

The gallbladder is the major site of **bile storage.** Upon eating, vagus nerve stimuli cause the gallbladder to contract and the sphincter of Boyden to relax in order to allow for release of bile into the common bile duct.

Bilirubin

Bilirubin is a product of heme metabolism (see Figure 3-21).

FLASH BACK

Drugs absorbed by the small intestine are subject to **"first-pass metabolism"** by the liver.

KEY FACT

Functions of hepatocytes:

- Formation of bile and bile pigments
- Production of serum proteins (albumin)
- Uptake of chylomicrons
- Production of plasma lipoproteins
- Drug, vitamin, and hormone metabolism
- Vitamin and mineral storage

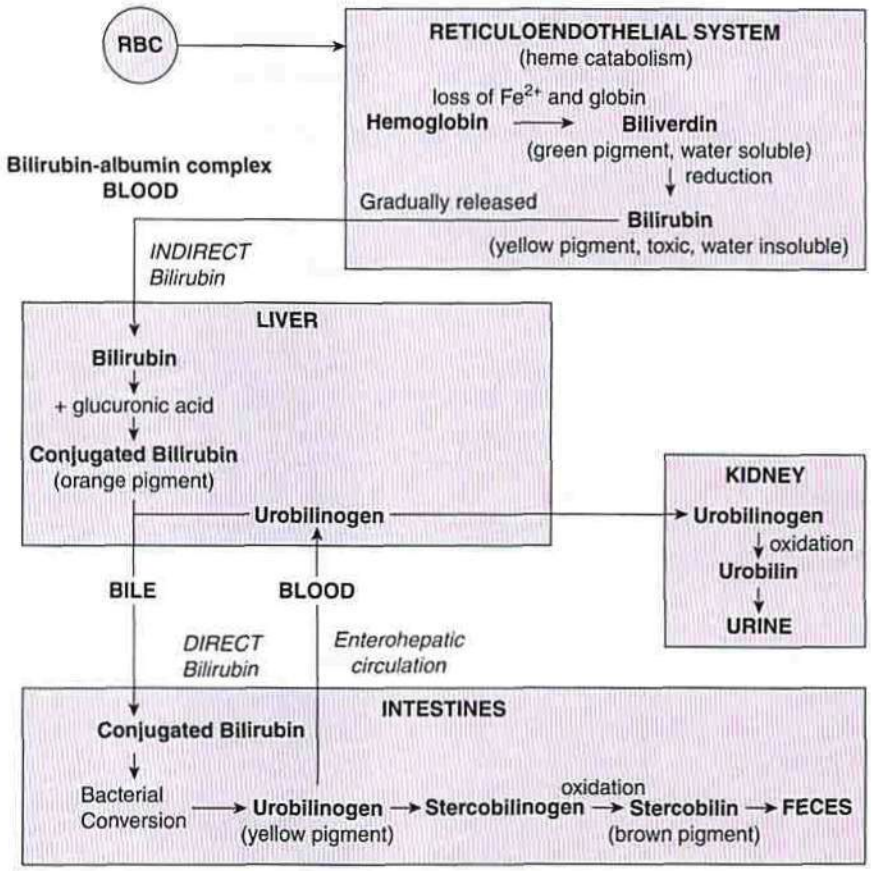


FIGURE 3-21. Bilirubin pathway.

FLASH FORWARD

Cholelithiasis (gallstones) are typically caused by excess cholesterol within the gallbladder. They can also result from precipitated calcium or bilirubin.

In the Reticuloendothelial System (RES)

The body produces approximately 250–300 mg of heme daily, chiefly from the breakdown of senescent RBCs. A smaller portion comes from turnover of hepatic heme, hemoproteins, and premature destruction of RBCs in the bone marrow (an important clinical consideration with hematologic disorders involving intramedullary hemolysis).

- Normally, heme is oxidized to **biliverdin** by heme oxygenase, and then reduced to bilirubin by biliverdin reductase.

In the Liver and Gallbladder

- **Unconjugated bilirubin (indirect bilirubin)** is transported to the liver in the bloodstream bound to albumin, as it is insoluble at physiologic pH.
- **In the liver,** hepatocytes take up bilirubin by carrier-mediated processes. It is then transported to the endoplasmic reticulum (ER) and **conjugated** with glucuronic acid by bilirubin uridine diphosphate (UDP)-**glucuronyltransferase.**
- **Conjugated bilirubin (direct bilirubin),** now in a water-soluble form, is excreted into bile.
- **Conjugated bile** is excreted into the intestines and is **not taken up** by the intestinal mucosa.

In the Colon

- Normal gut bacteria **hydrolyze** the majority of conjugated bilirubin to an unconjugated form called **urobilinogen** (~80%–90% is excreted in the stool; ~10%–20% is passively absorbed in the terminal colon, where it enters the portal venous system and is recycled by the liver).

In the Kidneys

- A small fraction of conjugated bilirubin is filtered by the kidney and excreted in the urine.

Bile

Produced by hepatocytes, bile is excreted into the bile canaliculi, where it travels down the bile ducts until it reaches the hepatic and common bile ducts. At this point, it is either excreted or stored in the gallbladder. Bile has **two main functions**:

- Helps to **emulsify** large fats, thus aiding in their absorption by the small intestine.
- Serves as a means of excretion of excess cholesterol and bilirubin.

There are several steps in bile synthesis (see Figure 3-22):

- **Primary bile acids** are synthesized in the liver from cholesterol.
- **Cholesterol** is first converted into **cholic acid** (chenodeoxycholic acid) and then **conjugated** with either glycine or taurine to form bile acids.
- These glycol- and tauro-conjugated bile acids acquire sodium to become bile salts so they can be secreted into the GI tract.
- Bile is recycled in the ileum, where it is transported back up into the hepatocytes via the enterohepatic cycle.

Secondary bile acids are the result of bacterial metabolism of primary bile acids that have been recirculated via the enterohepatic cycle.

Composition of bile:

- Bile salts
- Phospholipids
- Cholesterol
- Lecithin
- Water
- Bilirubin
- Ions

Pathology

ORAL CAVITY

Mouth and Jaw

Tumors are the most common pathologic finding in the mouth. Smoking is the greatest risk factor for oral cancer.

- **Premalignant lesions** are often difficult to identify since they lack the classic characteristics of advanced cancer: pain, ulceration, induration, and cervical lymphadenopathy.

CLINICAL CORRELATION

The kidney is **unable** to filter **unconjugated bilirubin** (urobilinogen); therefore, **any** bilirubin found in the urine indicates liver disease.

FLASH FORWARD

Jaundice (icterus) is a yellowing of the skin and sclerae due to elevated bilirubin levels.

- **Increased indirect bilirubin** indicates excess hemolysis or severe liver damage.
- **Increased direct bilirubin** indicates a blockage of the bile ducts.

KEY FACT

Secretin stimulates the liver to produce bile.

KEY FACT

CCK = Primary stimulating regulator of bile excretion.

KEY FACT

Somatostatin = Primary inhibiting regulator of bile excretion.

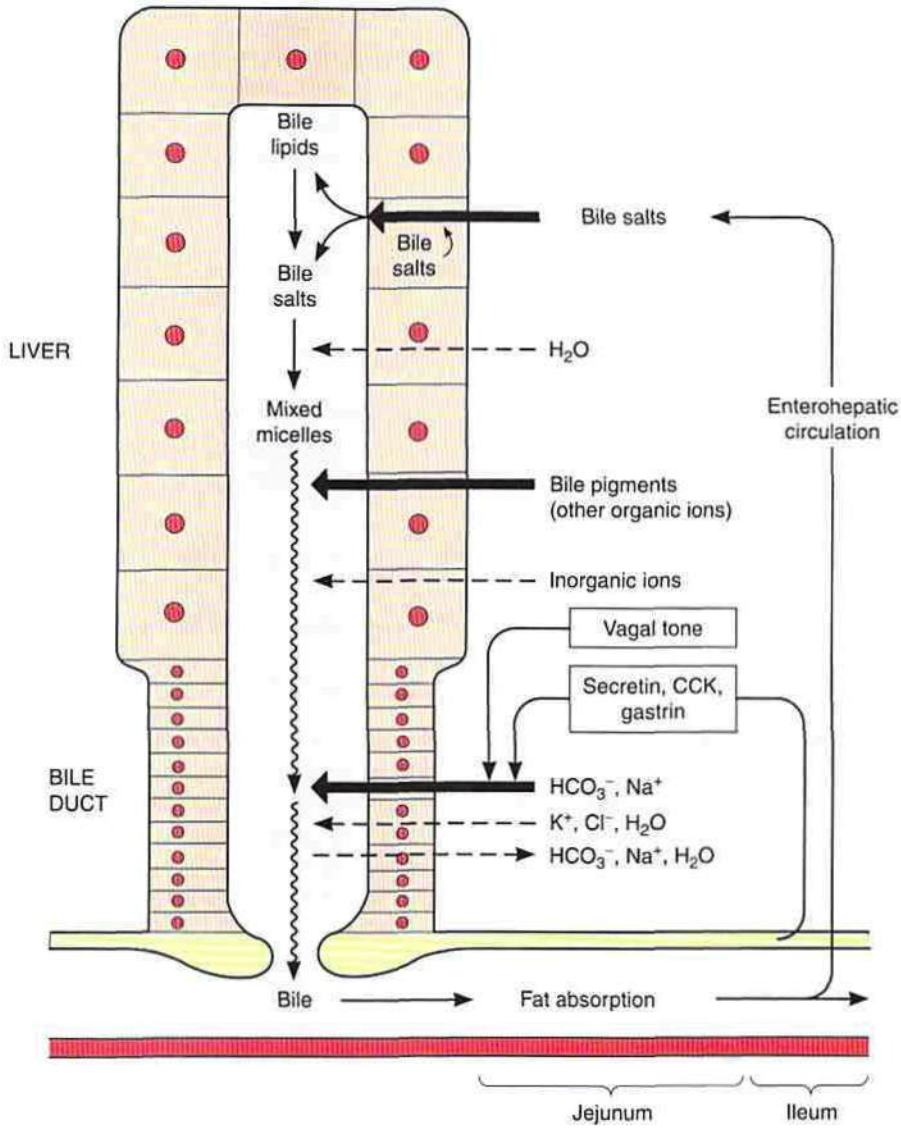


FIGURE 3-22. Bile formation. Solid lines into the ductular lumen indicate active transport; dotted lines represent passive diffusion. (Modified, with permission, from Doherty GM, Way LW, *Current Surgical Diagnosis and Treatment*, 12th ed, New York: McGraw-Hill, 2006: 576.)

- The most common **malignant lesion** is oral **squamous cell carcinoma (SCC).** Risk factors include chronic cigarette smoking and alcohol use.

One difficult task is distinguishing the premalignant lesion **leukoplakia** from more benign processes such as **lichen planus** and **candidiasis,** all of which present as white patches in the mouth, usually on the tongue.

- **Leukoplakia** (see Figure 3-23) is **squamous cell hyperplasia,** which can develop into dysplasia, carcinoma-in-situ, and invasive carcinoma. It can also be seen in inflammatory conditions unrelated to malignancy.
  - **Hairy leukoplakia** is a distinct inflammatory condition affecting immunocompromised patients (**pre-AIDS–defining condition**).
- **Lichen planus** is a self-limiting disease of unknown etiology that causes classic Wickham's striae, which are white lace-like patterns on top of papules or plaques.



FIGURE 3-23. Hairy tongue. Filiform hyperkeratoses of the papillae result in a brownish coating on the dorsum of the tongue in this 31-year-old cigarette smoker. (Reproduced, with permission, from Wolff K, Johnson RA, Suurmond R, *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed, New York: McGraw-Hill, 2005: 1019.)

- Oral **candidiasis** (see Figure 3-24) is essentially a yeast infection in the mouth; commonly seen in breast-feeding infants or **immunocompromised hosts.**

Characteristic pathologic findings and treatments are described in Table 3-9.

FLASH BACK

CDC category "B," pre-AIDS–defining conditions seen in the mouth:

- Hairy leukoplakia, an inflammatory condition caused by Epstein-Barr virus.
- Oral thrush
- Herpetic stomatitis and herpes esophagitis; caused by herpes simplex virus.

Salivary Glands

Sjögren's syndrome, an autoimmune condition, is the most notable disease affecting the salivary glands. Other important conditions include salivary stones, benign and malignant tumors, and infections such as mumps (depicted in Table 3-10).



FIGURE 3-24. Oral candidiasis (thrush). Extensive cottage cheese-like plaques, colonies of *Candida* that can be removed by rubbing with gauze (pseudomembranous), on the palate and uvula of an individual with advanced HIV disease. Patches of erythema between the white plaques represent erythematous (atrophic) candidiasis. Involvement may extend into the esophagus and be associated with dysphagia. (Reproduced, with permission, from Wolff K, Johnson RA, Suurmond R, *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed, New York: McGraw-Hill, 2005: 723.)

TABLE 3-9. Most Common Pathologies Affecting the Mouth and Jaw

	Presentation	Diagnosis	Treatment	Prognosis
SCC	Persistent papules, plaques, erosions, ulcers.	Biopsy with TNM staging.	Combination of surgery, radiation, and chemotherapy, depending on stage.	Related to stage and often diagnosed at a late stage; often recurs, even if caught early.
Leukoplakia	White patches or plaques on oral mucosa.	Biopsy.	Surgery, cryotherapy ablation, carbon dioxide laser ablation.	1%–20% of lesions will progress to malignancy in 10 years.
Melanoma	Oral lesion with asymmetry, irregular borders, color changes, increasing diameter.	Biopsy.	Surgical resection with negative margins and radiation if negative margins are not obtained.	Depends on stage, including tumor thickness and ulceration.
Oral candidiasis (thrush)	White plaque that can be scraped off.	Confirmed with KOH prep.	Nystatin mouthwash for 7–10 days.	Can be recurrent in the immunocompromised.
HSV-1 herpetic stomatitis	Vesicular lesions with erythematous bases.	Multinucleated giant cells on Tzanck smear.	Acyclovir, pain management, fluids.	Will recur; some patients have success with chronic suppression.
Aphthous ulcers	Localized, shallow, round ulcers with gray bases that heal in 7–14 days.	Clinical presentation.	Symptomatic relief with oral analgesics.	Some patients have recurrent aphthous stomatitis.

Sjögren's Syndrome (Xerostomia; Keratoconjunctivitis Sicca)

Can occur independently or in conjunction with another autoimmune condition, such as rheumatoid arthritis or systemic lupus erythematosus (SLE).

- The hallmark of this syndrome is lymphocytic infiltration of exocrine glands, most notably the salivary and lacrimal glands, resulting in the classic findings of dry mouth and dry eyes.

FLASH FORWARD

Hallmarks of Sjögren's syndrome are dry eyes (**keratoconjunctivitis sicca**) and dry mouth (**xerostomia**) along with multisystem involvement, including skin, lung, heart, and kidney.

Diagnosis

The presence of **anti-Ro/SSA** or **anti-La/SSB antibodies** is indicative of Sjögren's syndrome.

- **Schirmer's test,** which is a measure of tear production.
- **Rose bengal stain** can also show areas of corneal or conjunctival epithelial cell damage.
- A **salivary gland biopsy** from the lip may show focal collections of lymphocytes.

Treatment

KEY FACT

Patients with Sjögren's syndrome have an increased risk of lymphoma.

- **Symptomatic:** Eye drops for keratoconjunctivitis sicca and the use of sugarless candy or lozenges containing malic acid to stimulate the production of saliva.
- **Good oral hygiene and dental care** due to an increased risk of dental caries, gum disease, and halitosis. May also help to prevent salivary calculi, dysphagia, and oral candidiasis.

TABLE 3-10. Most Common Diseases of Salivary Glands

	Etiology/Presentation	Diagnosis	Treatment	Prognosis
Mumps	Paramyxoma virus (parotiditis, fever, myalgias, headache, anorexia), and can cause orchitis.	Positive IgM mumps antibody, rise in IgG titers, isolation of mumps virus.	Symptomatic: analgesics and antipyretics.	Vaccination; patients with meningitis or pancreatitis require hospitalization.
Hypertrophy	Can be caused by eating disorders (bulimia), kwashiorkor, alcoholism, and metabolic disease.	Clinical observation.	Treat underlying disease.	
Sialolithiasis (salivary stones)	▪ Submandibular glands; more common in men. ▪ Forms when saliva rich in calcium is stagnant. ▪ Some association with gout and nephrolithiasis.	Palpation of salivary ducts or imaging studies if not palpable.	Conservative therapy: hydration (and sucking on candy to increase salivation), moist heat, massaging the gland, and milking the duct.	Secondary infection; chronic sialolithiasis may indicate dysfunctional gland.
Salivary gland tumors	▪ Risk factors: radiation and EBV. ▪ Smoking has not been connected to malignant tumors, but is linked to benign papillary cystadenoma lymphomatosum. ▪ Most common tumor is **pleomorphic adenoma** (mixed tumor), affecting parotid glands.	Fine-needle aspiration with TNM staging biopsy, CT, MRI.	▪ Benign: Superficial or total parotidectomy. ▪ Malignant: Wide surgical margins, neck dissection, depending on level of involvement; chemotherapy.	If malignant 20% recurrence rate after 5 y; rare after 10–20 y.

- More severe cases may require **pilocarpine**, a muscarinic agonist that stimulates salivation and has side effects of sweating, abdominal cramping, and flushing.

ESOPHAGUS

Esophageal Atresia (EA) and Tracheoesophageal Fistula (TEF)

The most common congenital anomaly of the esophagus, often associated with TEF (connection between the trachea and esophagus). EA creates a blind pouch of esophagus because it does not maintain the tubular structure.

There are several forms of EA, many with TEF (see Figure 3-25). Each type depends on the anatomy of the esophagus and the presence or absence of a fistula.

KEY FACT

In the most common form of EA/TEF, (type III; see Figure 3-28C), the proximal esophagus ends in a blind pouch, while the distal esophageal segment demonstrates a proximal TEF.

Presentation

Depends on the type of EA/TEF:

- Neonates typically present very early with frothing and bubbling at the nose and mouth as well as coughing, cyanosis, and respiratory distress exacerbated by feeding.
- Children who have TEF but no EA can present later in life with recurrent pneumonia from the aspiration of gastric contents.

CLINICAL CORRELATION

Maternal polyhydramnios develops as a consequence of EA. This is also indicative of duodenal atresia and Down's syndrome.

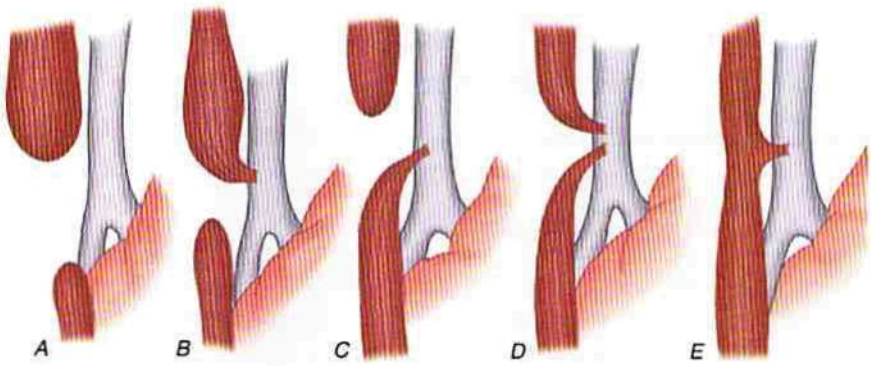


FIGURE 3-25. The five varieties of EA and tracheoesophageal fistula. (A) Isolated EA. (B) EA with tracheoesophageal fistula between proximal segments of esophagus and trachea. (C) EA with tracheoesophageal fistula between distal esophagus and trachea. (D) EA with fistula between both proximal and distal ends of esophagus and trachea. (E) Tracheoesophageal fistula without EA (H-type fistula). (Modified, with permission, from Brunicardi FC, Andersen DK, Billiar TR, *Schwartz's Principles of Surgery*, 8th ed, New York: McGraw-Hill, 2005: 1481.)

Diagnosis

The diagnosis is confirmed by trying to pass a nasogastric tube into the stomach. If it does not pass easily, an anteroposterior chest radiograph will show the catheter coiled in the blind pouch.

- **Distal TEF** can be diagnosed by a gas-filled GI tract on plain film.

Treatment

Surgical correction

- **Long-term complications:** Organ-related: GERD from intrinsic esophageal incompetence; surgical: anastomotic stricture and refistulization.

Prognosis

Depends on other associated chromosomal abnormalities (more complicated congenital malformations).

Esophageal Diverticula

Saccular outpouchings that can be found in the esophagus just as they are found in the colon.

- **False (pulsion) diverticula:** Mucosal layers protruding through the muscularis; most common type.
- **True (traction) diverticula:** Contains all layers of the esophageal wall; less common type.

CLINICAL CORRELATION

Zenker's and epiphrenic types of diverticula are commonly associated with **motor abnormalities** of the esophagus, such as spasm, achalasia, and UES/LES hyperactivity.

The three characteristic locations of the diverticula:

- **Pharyngoesophageal (Zenker's; pulsion) diverticulum** (see Figure 3-26): Located immediately above the cricopharyngeus muscle of the UES.
- **Midesophageal (traction) diverticula**: Usually located in the middle third of the esophagus. They are usually associated with inflammatory conditions such as TB.
- **Epiphrenic (pulsion) diverticula**: Located in the distal esophagus in the region of the LES.

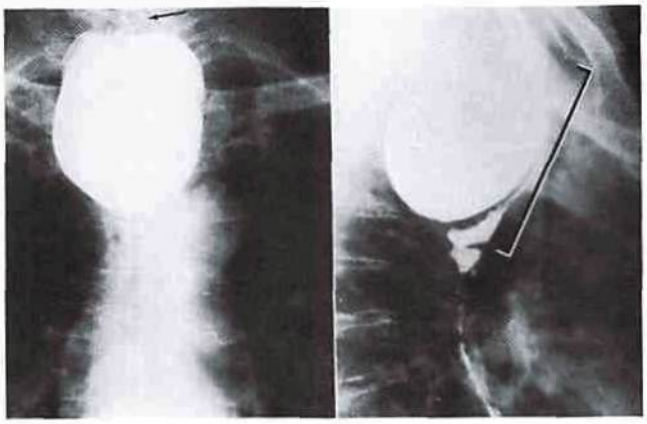


FIGURE 3-26. Large pharyngoesophageal diverticulum. Note origin in the midline (arrow, left) and compression of esophagus (bracket, right). (Reproduced, with permission, from Doherty GM, Way LW, *Current Surgical Diagnosis and Treatment*, 12th ed, New York: McGraw-Hill, 2006: 460.)

Diagnosis

Patients typically present in their 60s. The earliest sign is transient dysphagia. As the pouch enlarges, more debris is retained and patients can aspirate, complain of gurgling or **regurgitating undigested food,** or have a mass in the neck. The best diagnostic technique is a barium swallow.

Treatment

Surgical treatment depends on type and location.

- Traction diverticula rarely require surgical treatment.
- For Zenker's and epiphrenic diverticula, surgical treatment includes division of the cricopharyngeus muscle (Zenker's) and distal esophageal myotomy (epiphrenic) with diverticulectomy.
- Perioperative morbidity may include mediastinitis, vocal cord paralysis, fistulas, and recurrence.

Esophageal Varices

Develop as a consequence of portal hypertension. Venous dilation occurs in response to increased **portal venous pressure** (>12 mmHg). Veins are thinner walled in the distal esophagus and are thus more prone to bleeding. Variceal bleeding is an important cause of upper GI bleeds in alcoholics and other people with cirrhotic livers.

KEY FACT

Portal hypertension leads to stasis, and the resulting increased pressure in the left gastric vein leads to esophageal varices.

Diagnosis

Via endoscopy; sometimes difficult to detect during active variceal hemorrhage.

Treatment

Current treatments include:

- **Vasopressin:** Vasoconstriction of mesenteric vessels, which decreases portal venous flow. Good for initial management, but does not prevent rebleeding.
- **Somatostatin or octreotide:** Inhibits release of vasodilating hormones (e.g., glucagons), indirectly causing vasoconstriction.

- **Endoscopy:** Definitive treatment, either sclerotherapy or variceal band ligation.
- **Balloon tamponade** can provide short-term hemostasis.
- Transjugular intrahepatic portosystemic shunt.

Achalasia

Defined as **"failure to relax,"** achalasia is characterized by:

- Aperistalsis (required for diagnosis).
- Incomplete relaxation of the LES with difficulty swallowing (often associated, but not required for diagnosis).
- Increased resting tone of the LES (often associated, but not required for diagnosis).

Achalasia can be due to primary (most common) or secondary causes.

- **Primary achalasia** develops as a result of the **absence of ganglionic cells** in the myenteric plexus, which causes persistent contraction of the LES, thus leading to progressive dilation of the distal esophagus.
- **Secondary achalasia** occurs from any pathologic process that impairs esophageal motility.
  - **Chagas' disease** (principal cause of achalasia in South America) develops as a result of infestation with *Trypanosoma cruzi*, which destroys the myenteric plexus of the esophagus, duodenum, colon, and ureter.
- **Achalasia-like conditions** can occur with amyloidosis, sarcoidosis, or carcinoma.

CLINICAL CORRELATION

Difficulty in swallowing **both** solid and liquid food indicates a **motility (neuromuscular) problem.** Difficulty in swallowing **solid food only** indicates an **anatomic (mechanical) problem.**

CLINICAL CORRELATION

Differential diagnosis of distal esophageal narrowing includes esophageal cancer.

CLINICAL CORRELATION

Patients with difficulty swallowing, (especially those > 50 years), should undergo **endoscopy** to rule out cancer.

KEY FACT

Distinguish GERD from physiologic postprandial reflux by noting mucosal damage and nocturnal symptoms.

Presentation

Classically affects young adults, but also frequently affects infants or children. Presents with progressive dysphagia and frequent nocturnal regurgitation and/or aspiration of undigested food.

Diagnosis

Clinical presentation (progressive dysphagia). Manometry will show normal or elevated resting LES pressure, decreased LES relaxation, and **absence** of peristalsis. Classic imaging findings associated with achalasia include:

- Dilated esophagus with distal **bird-beak**–like narrowing on **barium swallow** imaging (see Figure 3-27).
- Disorganized tertiary contractions of the esophagus during fluoroscopy.

Treatment

Distal esophageal myotomy with or without partial gastric fundoplication, or endoscopic pneumatic balloon dilation.

Gastroesophageal Reflux Disease

Also known as **reflux esophagitis**, GERD develops as a result of abnormal relaxation of the LES and/or delayed gastric emptying with increased pressure in the stomach (e.g., hiatal hernia or pregnancy). These abnormalities allow gastric contents to reflux into the esophagus, thus leading to esophageal injury, and if left untreated, chronic inflammation.



FIGURE 3-27. Bird-beak esophagus typical of achalasia. Aperistalsis of the esophagus was present associated with smooth narrowing at the lower end of the esophagus (arrow), suggesting achalasia of the esophagus. (Reproduced, with permission, from Chen MYM, Pope TL, Ott DJ, *Basic Radiology*, New York: McGraw-Hill, 2004: 258.)

Diagnosis

Symptoms of GERD include heartburn, water brash (an acidic taste in the mouth), dysphagia, hoarseness, globus sensation (lump in the throat), chronic cough (especially at night), and regurgitation. Definitive diagnosis is established with endoscopic observation of mucosal changes. For some patients, pH monitoring may be required. A **triad of histologic features** indicative of mucosal inflammation is key to a GERD diagnosis:

- Eosinophils (advanced cases show neutrophils)
- Basal zone hyperplasia
- Elongation of the lamina propria papillae

CLINICAL CORRELATION

Adult-onset asthma is often associated with GERD.

Treatment

Lifestyle and diet changes (smoking cessation; avoidance of alcohol and caffeine, fatty foods, acidic foods, spicy foods, and chocolate), antacids, and over-the-counter histamine H_2-blockers for heartburn. More advanced disease requires pharmacologic acid suppression with histamine blockers or proton pump inhibitors. GERD usually improves with medication (80%–90% of cases). GERD that is incompletely controlled by medication and lifestyle changes can be treated surgically with gastroesophageal fundoplication (Nissen fundoplication).

Prognosis

Long-standing reflux can predispose to Barrett's esophagus, which can ultimately develop into adenocarcinoma of the esophagus (see Figure 3-28).

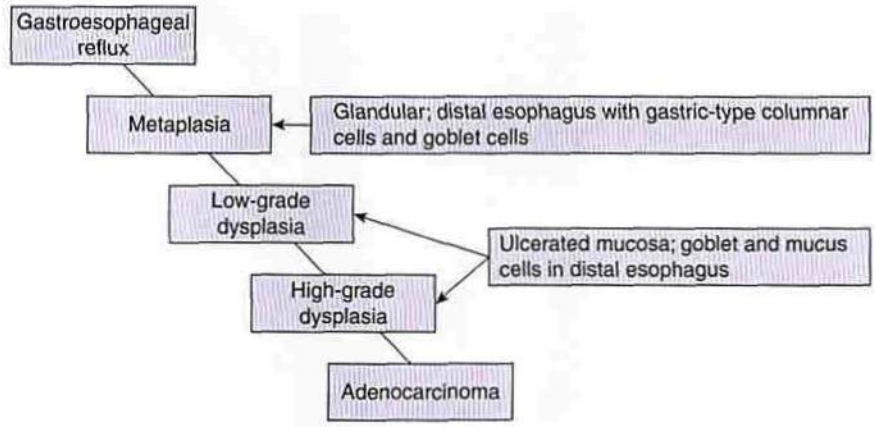


FIGURE 3-28. Progression from gastroesophageal reflux disease to Barrett's esophagus and adenocarcinoma.

Barrett's Esophagus

A precancerous lesion of the distal esophagus and a complication of long-standing GERD. It occurs when esophageal mucosa undergoes metaplasia from squamous to specialized columnar cells containing goblet cells (i.e., intestinal metaplasia; see Figure 3-29). Gastric-type columnar cells may be present, but are not diagnostic of Barrett's esophagus. Incidence is highest in white males.

PRESENTATION

Patients 40–60 years old with a history of several years of symptomatic GERD. Advanced cases may present with progressive (weeks to months) dysphagia for solids, weight loss, cough, and/or regurgitation/aspiration (worse at night).



FIGURE 3-29. Histology of esophageal adenocarcinoma associated with Barrett's esophagus. High-grade dysplasia with early intramucosal carcinoma. (Image courtesy of PEIR Digital Library [http://peir.net].)

Diagnosis

Based on endoscopy and biopsy findings:

- **Endoscopy:** Red, velvety GI mucosa extending upward from the gastroesophageal junction, in contrast to the normal pale pink squamous epithelial mucosa of the esophagus.
- **Biopsy:** Intestinal-type goblet cells in the columnar mucosa of the esophagus.

Treatment

Regular endoscopic surveillance for at-risk patients along with aggressive medical or surgical treatment of GERD. Patients with Barrett's esophagus and high-grade dysplasia typically undergo esophagectomy due to the high risk of esophageal cancer.

Prognosis

Complications of Barrett's esophagus include strictures, peptic ulceration, and the potential for malignant transformation into adenocarcinoma.

Esophageal Cancer

The incidence varies greatly, depending on geographic region, suggesting environmental causative factors. In the United States, it is more common in blacks than whites, males, and those with lower socioeconomic status. There are two major types:

- **SCC:** Linked to smoking, alcohol consumption (liquor > beer), nitrites, smoked opiates, fungal toxins, radiation, and lye exposure.
- **Adenocarcioma:** A result of chronic GERD leading to intestinal metaplasia of stratified nonkeratinized esophageal epithelium (Barrett's esophagus), which leads to dysplastic changes in the columnar epithelium and adenocarcinoma (see Figures 3-29).

Presentation

Typically, SCC appears in the upper and middle esophagus, while adenocarcinoma appears in the lower esophagus. Most common presenting symptoms are dysphagia and weight loss. The disease is usually incurable once dysphagia is present, as > 60% of the esophageal circumference is involved. Other symptoms include odynophagia, emesis, and aspiration secondary to tracheoesophageal fistula formation.

- Cancer **typically spreads locally** to surrounding tissue, lymph nodes, lungs, liver, and pleura.

Diagnosis

Periodic screening endoscopy is recommended in high-risk patients with biopsy of suspicious lesions.

- **Contrast radiography:** Identifies esophageal strictures, ulcerations, and mucosal abnormalities with a ragged, ulcerated appearance (see Figure 3-30). However, only high-grade lesions are seen with this approach.

Treatment

Esophagectomy for potentially curable lesions with or without preoperative chemotherapy and radiation therapy. Palliative treatment for symptomatic advanced-stage lesions (stricture balloon dilation and esophageal stent placement).

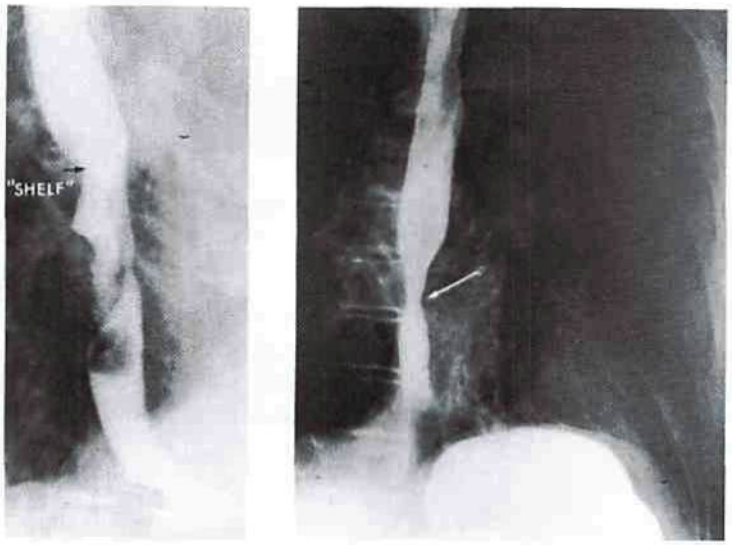


FIGURE 3-30. Radiographs of the two most common types of esophageal carcinoma. Fungating (left) and annular (right). (Reproduced, with permission, from Doherty GM, Way LW, *Current Surgical Diagnosis and Treatment*, 12th ed, New York: McGraw-Hill, 2006: 470.)

Prognosis

Tumor resection, chemotherapy, and radiation therapy are used in some patients to reduce tumor burden, but these are rarely curative. Survival rate 5 years after diagnosis is around 25%.

STOMACH

Gastritis

Gastritis is an inflammation of the gastric mucosa. Depending on the cause, type, and duration of inflammation, it can be subdivided into acute and chronic types.

CLINICAL CORRELATION

Gastritis

- Acute erosive gastritis is a major cause of hematemesis.
- Excessive NSAID use and excessive alcohol use are common causes of hemorrhagic gastritis.
- **All forms** of chronic gastritis confer an increased risk of **gastric adenocarcinoma.**
- Type B results in increased risk of mucosa-associated lymphoid tissue **(MALT) lymphomas.**

Acute Gastritis

Acute, transient mucosal damage with mucosal edema and inflammation (see Figure 3-31). The injury might erode the mucosa and affect underlying epithelium, in which case **hemorrhagic gastritis** develops. Most common causes include:

- NSAID overuse
- Alcohol consumption
- **Cushing's ulcers** associated with head trauma
- **Curling's ulcers** associated with burns
- Uremia
- **Stress-induced gastritis:** Hemoccult-positive stools and visible changes on endoscopic examination of the stomach.

Chronic (Atrophic) Gastritis

Continuous inflammation of the gastric mucosa leads to mucosal atrophy and epithelial metaplasia (hence "chronic" and "atrophic"). Based on the location of the injury and the causative agent, chronic gastritis is divided into **types A** and **B.**

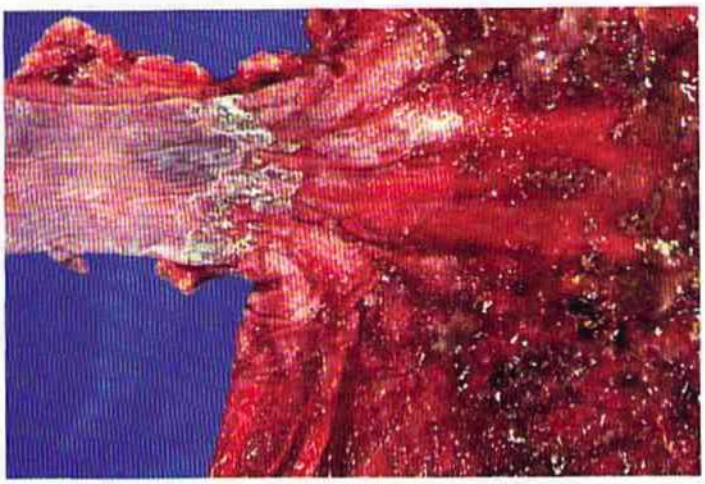


FIGURE 3-31. Acute erosive gastropathy, showing multiple gastric ulcerations. On biopsy, there would be evidence of mucosal damage but no neutrophils or lymphocytes. (Image courtesy PEIR Digital Library [http://peir.net].)

- **Type A:** Affects the fundus and body of the stomach (see Figure 3-32) and spares the antrum. Typically secondary to pernicious anemia (also known as autoimmune gastritis). It is associated with antibodies to the parietal cells (specifically targeting H^-, K^+-ATPase) and to the IF. It leads to achlorhydria with consequent hypergastrinemia.
- **Type B:** Antral predominant, sparing the fundus and body. Typically secondary to chronic *Helicobacter pylori* infection.

FLASH BACK

Mucosal damage develops due to the erosive nature of ammonia, which is a product of urea degraded by the urease produced by *H. pylori.*

PRESENTATION

Abdominal pain, dyspepsia, and visual changes noted on endoscopic inspection **do not reliably correlate** with the histopathologic diagnosis of gastritis.

FLASH FORWARD

Decreased availability of IF in autoimmune gastritis ultimately leads to pernicious anemia.

DIAGNOSIS

Can only be confirmed histologically (biopsy).

- Diagnosis of *H. pylori* infection is based on biopsy (will show gram-negative rods), **urease breath test,** and **stool and serum antigens** (see the section on peptic ulcer disease [PUD]for further discussion).

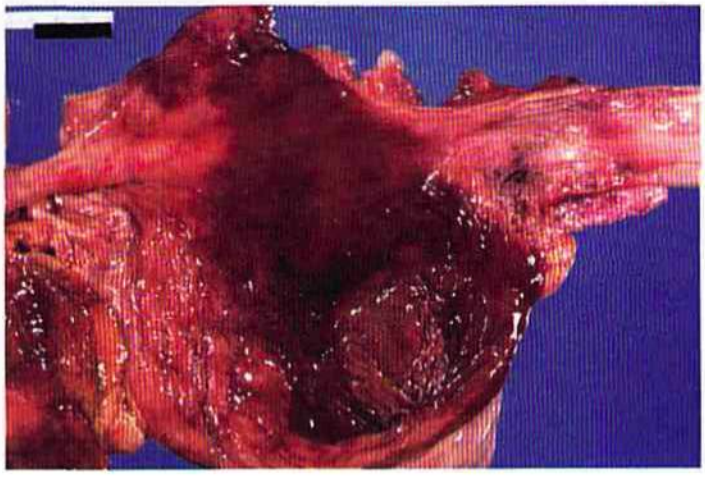


FIGURE 3-32. Type A chronic gastritis with changes mainly in the fundus of the stomach. (Image courtesy of PEIR Digital Library [http://peir.net].)

- Pernicious anemia is always suspected in patients with megaloblastic anemia, chronic neurologic changes, and an **abnormal Schilling test.**

Treatment

Aimed at treatment of the sequelae, rather than the causative agent.

- For treatment of *H. pylori*, see the section on PUD.
- Patients with pernicious anemia need **parenteral** vitamin B_{12} supplementation.
- Proton pump inhibitors are normally given to patients in the ICU or those who have suffered head trauma or burns as prophylaxis against acute erosive gastritis.

Ménètrier's Disease

Hyperplasia of mucus-secreting cells resulting in rugal hypertrophy and **hypoproteinemia.** Also causes atrophy of parietal cells, thus resulting in achlorhydria. Patients are at risk for adenocarcinoma.

Peptic Ulcer Disease (PUD)

Ulcer formation in the stomach or the first part of the duodenum is secondary to mucosal disruption.

Gastric mucosal cells secrete mucus with large quantities of **bicarbonate** in order to maintain a **pH of 6–7 around the epithelial cells,** in contrast to the pH of **1–2** in the **gastric lumen.** When the mucus layer is breached, either by drugs, bacteria, or systemic disorders, epithelial injury occurs and ulcers can form.

Gastric Ulcers

Less common and occur later in life. Typically develop along the lesser curvature, in the **antral** and **prepyloric** regions. Malignant transformation is **more common** than with duodenal ulcers. They are primarily caused by *H. pylori*. Basal and nocturnal acid secretion is typically normal to **decreased.**

Duodenal Ulcers

More than 95% occur in the first portion of the duodenum. Ulcers are typically greater than 1 cm in size, and **malignancy is extremely rare.** Basal and nocturnal acid secretion tends to be **increased.** NSAIDs and *H. pylori* are also associated risk factors.

The gross appearance is a clean, sharply demarcated ulceration (see Figure 3-33), and **unlike ulcerated cancers,** the edges are only slightly elevated.

Presentation

Burning, gnawing epigastric pain is typical but not specific for this diagnosis (see Table 3-11).

- Patients with **duodenal ulcers** tend to give a history of pain **2–3 hours after** meals that is **relieved with food.**
- Patients with **gastric ulcers** have increased **pain with food,** as well as nausea and weight loss.

On physical exam, patients can have tenderness to palpation in the epigastric region. Abdominal rigidity and peritoneal signs are concerning for perfora-

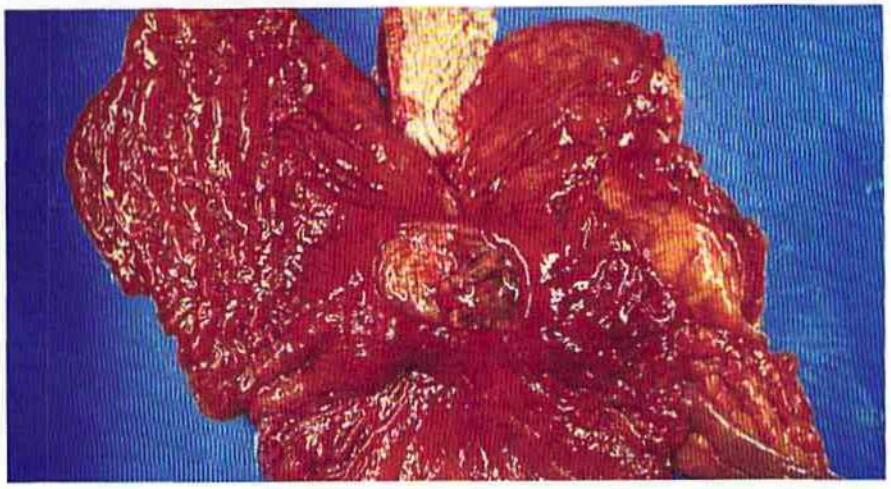


FIGURE 3-33. Gastric ulcer. Note sharply demarcated edges, clean base, and minimal elevation of the edges. (Image courtesy of PEIR Digital Library [http://peir.net].)

tion (most common with duodenal ulcers), which can lead to peritonitis. The most common complication is **upper GI bleeding** and presents as melena or hematemesis.

Diagnosis

In addition to the rather nonspecific history and physical exam:

- **Contrast radiography** can show defects in the gastric and duodenal epithelium caused by ulcers, although small erosions are typically missed.
- *H. pylori* must also be excluded, as a large number of cases are secondary to this common bacterium. Tests include serum antibodies (**not useful in confirming successful treatment**), stool antigen (**useful in confirming eradication**), urease breath test, and biopsy of tissue via esophagogastroduodenoscopy.

CLINICAL CORRELATION

Perforated duodenal ulcer often presents with epigastric pain radiating to the left shoulder as well as with air under the diaphragm.

TABLE 3-11. The Most Common Characteristics of PUD

	Gastric Ulcer	Duodenal Ulcer
Percentage	25%.	75%.
Common causes	*Helicobacter pylori* (~80%), NSAID use.	*H. pylori* (90%–95%), NSAID use.
Presenting symptoms	Pain with food.	Pain 2–3 h after meals and relived by food.
Complications	Perforation, bleeding, malignancy, gastric outlet obstruction.	Perforation, bleeding, gastric outlet obstruction, pancreatitis.
Malignancy	10%.	Rare.
Location	Type-dependent; typically lesser curvature.	First portion of duodenum.

Treatment

If secondary to chronic NSAID use, the medication should be discontinued or limited. Lifestyle changes such as discontinuing alcohol and tobacco are also helpful if ulcers are thought to be secondary to these drugs. *H. pylori* should be treated if the patient is found to be infected.

- One well-accepted current treatment recommendation is **clarithromycin + amoxicillin + PPI ± bismuth subsalicylate for 10–14 days.**
- For gastric ulcer, biopsy should be performed at the margin of the ulcer to rule out malignancy.

Gastric Cancer

Gastric cancer is a malignant tumor that is the second most common cause of cancer-related death worldwide. Histologically, about 85% are adenocarcinomas, while the remaining 15% are lymphomas and leiomyosarcomas.

Adenocarcinoma

There are two types of adenocarcinoma:

- **Intestinal type:** Thought to arise from the intestinal metaplasia of gastric mucosal cells. Lesions are typically ulcerative and occur in the antrum and lesser curvature (see Figure 3-34). Risk factors are a diet high in salt and nitrates, *H. pylori* colonization, and chronic gastritis.
- **Diffuse type:** Cells lack normal cohesion, resulting in an infiltrating, discrete mass in the stomach wall. They are more common in younger patients, involve all portions of the stomach, and result in decreased motility, hence, the term **linitis plastica** or **"leather bottle"** appearance.
  - **Krukenberg's tumor** is a diffuse type of gastric metastasis to the ovaries with **signet ring** histology (see Figure 3-35).

Primary Gastric Lymphoma

The stomach is the most common extranodal site for lymphoma formation, often associated with *H. pylori* infection. Histology ranges from low-grade (MALT lymphomas) to high-grade large cell non-Hodgkin's lymphomas.

Presentation

Asymptomatic until metastasis or incurable extensive growth has occurred. **Advanced cases** present with insidious upper abdominal pain, postprandial fullness, early satiety, weight loss, and nausea.

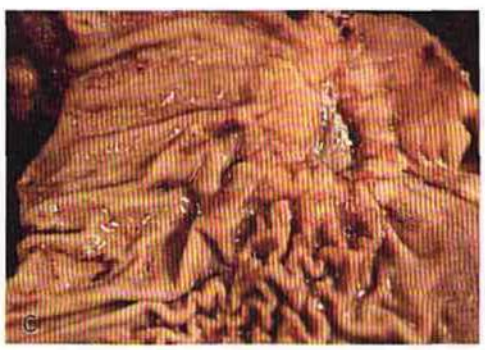


FIGURE 3-34. Advanced gastric cancer, intestinal type, showing typical raised margins and ulcerated base. (Image courtesy of PEIR Digital Library [http://peir.net].)

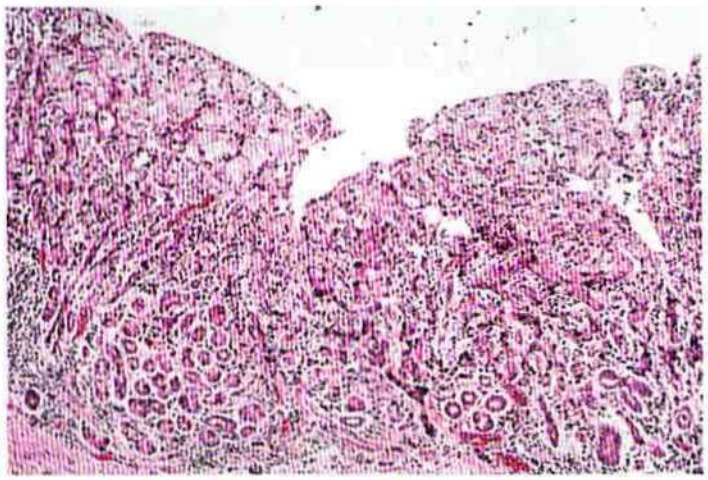


FIGURE 3-35. Primary signet ring neoplasm in mucosa. H&E stain. (Image courtesy of PEIR Digital Library [http://peir.net].)

- Typically spreads locally to adjacent organs (direct extension to porta hepatis and transverse colon) and peritoneum.
- Metastases to the left supraclavicular lymph node produces palpable lymphadenopathy **(Virchow's node)**.
- Hematogenous dissemination to the ovaries (**Krukenberg's** tumor).
- Metastases to the umbilicus produce **Sister Mary Joseph's sign.** This diagnosis should also be suspected in patients with acanthosis nigricans as well as multiple outcroppings of seborrheic keratoses **(Leser-Trélat sign).**

Diagnosis

Double-contrast radiographic examination and CT scan imaging (see Figure 3-36) can identify very small lesions. Lack of distention is also a clue to diffuse-type gastric cancer. Definitive diagnosis is established based on biopsy.

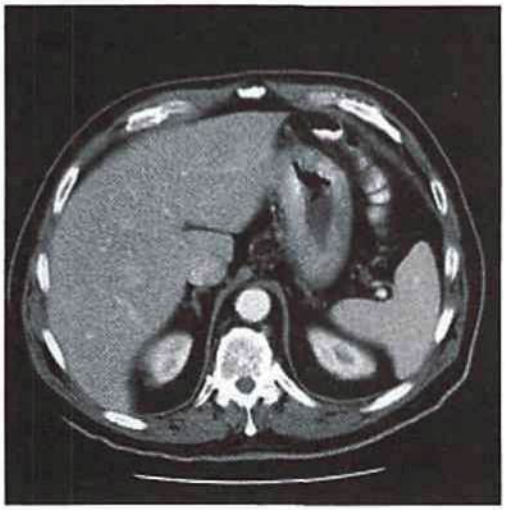


FIGURE 3-36. Adenocarcinoma of the stomach, diffusely infiltrative type, also known as linitis plastica. Wall thickening (with an adequately distended gastric lumen) and loss of the normal rugal folds may be seen on CT imaging. The abnormally thickened wall may exhibit enhancement after contrast administration. (Image courtesy of PEIR Digital Library [http://peir.net].)

Treatment

Surgical resection of involved gastric tissue and adjacent lymph nodes, along with radiation and chemotherapy.

Prognosis

- Prognosis for patients with **adenocarcinoma** is poor (5-year survival rate is 10%–20%).
- Prognosis for patients with **primary gastric lymphoma** is somewhat better (5-year survival rate is 40%–60%). *H. pylori* antibiotic therapy is often enough to treat MALT lymphomas, while subtotal gastrectomy with chemotherapy and radiation is used for higher-grade lymphomas.

SMALL AND LARGE INTESTINE

Malabsorption Syndromes

This group of disorders is characterized by **decreased intestinal absorption** of certain essential nutrients and **chronic diarrhea** with **steatorrhea** with consecutive systemic effects, such as weight loss and specific vitamin and mineral deficiencies, particularly the **lipid-soluble vitamins A, D, E, and K.**

Underlying pathophysiologies include:

- Pancreatic deficits (lack of lipase).
- Damage to the intestinal mucosal surface (surgical resection or pathologic insult to the intestinal villi).
- Liver deficiencies (inadequate bile salt production, abetalipoproteinemia).
- Decreased intestinal transit time.

CLINICAL CORRELATION

Steatorrhea is defined as **stool fat content > 6% of dietary fat intake** (not seen with pernicious anemia or lactate deficiency).

The spectrum of malabsorption syndromes includes celiac sprue, lactate deficiency, Whipple's disease, tropical sprue, short bowel syndrome, bacterial overgrowth syndrome, protein-losing enteropathy, pancreatic failure, and pernicious anemia.

Presentation

Slightly different for each disorder. However, in general, patients have chronic diarrhea or steatorrhea with an increased stool osmotic gap.

Diarrhea is classified as either **secretory** (e.g., enteropathogenic *Escherichia coli*) or **osmotic** (malabsorptive syndromes). To differentiate between the two types:

- Initiate a 24-hour fast (secretory diarrhea continues; malabsorptive diarrhea typically stops).
- Calculate the **stool osmotic gap:** $[2 \times (Na_{stool} + K_{stool})]$ **– calculated stool osmolality.**
  - Osmotic gap > 50 and presence of steatorrhea indicates malabsorption.
  - Osmotic gap < 50 means that diarrhea is likely inflammatory or secretory.

Celiac Sprue (Gluten-Sensitive Enteropathy)

Autoimmune entity with antibodies against the water-insoluble **gliadin** fraction of **gluten**, a protein found in wheat, barley, rye, and oats. Age at presentation varies, but it classically occurs in infants during the time of **cereal introduction.**



FIGURE 3-37. Dermatitis herpetiformis seen in celiac sprue, manifested by pruritic, grouped vesicles in a typical location. The vesicles are often excoriated and may occur on the knees, buttocks, and posterior scalp. (Reproduced, with permission, from Kasper DL, Braunwald E, Fauci AS, et al., eds, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 287.)

- Symptoms can be:
  - **Mild:** Single vitamin deficiency and chronic diarrhea.
  - **Severe:** Characteristic **chronic diarrhea** with steatorrhea and pale, bulky, foul-smelling stools; multiple vitamin and mineral deficiencies; weight loss; **growth retardation;** and **failure to thrive.**
  - Associated with **dermatitis herpetiformis** (see Figure 3-37).
  - In 80%–90% of cases, association with the human leukocyte antigens **(HLA)-B8** or **HLA-DW3.**
- **Classic pathohistologic findings:** Mucosal inflammation, villous atrophy (flattening), and crypt hyperplasia (see Figure 3-38). Primarily affects the duodenum and jejunum.

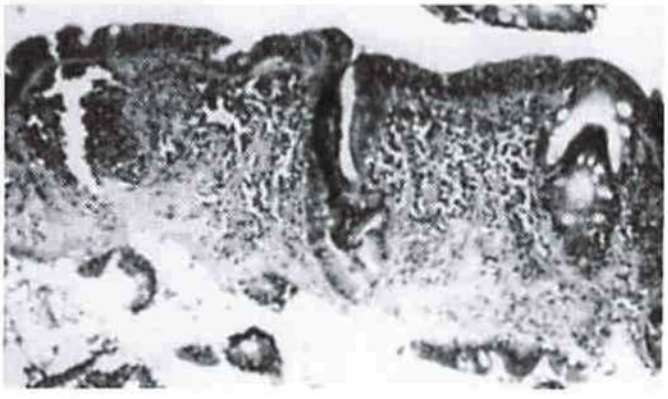


FIGURE 3-38. Total villous atrophy in a case of celiac disease. Note the flat surface epithelium without villi. The surface epithelium also appears more cuboidal, with less cytoplasmic mucin than is normal. The hypercellular appearance of the surface epithelium is due to the presence of numerous intraepithelial lymphocytes (visible only at higher magnification). (Reproduced, with permission, from Chandrasoma P, Taylor CR, *Concise Pathology*, 3rd ed, New York: McGraw-Hill, 2004.)

KEY FACT

Less common disaccharidase deficiencies are **sucrase** (table sugar) and **trehalase** (sugar found in mushrooms) deficiencies.

Disaccharidase Deficiency

The most common entity involves **lactase** (a brush border enzyme) deficiency and presents as dairy intolerance. It is rare as an inborn error, but is common during adulthood as the lactase present in the immature brush border disappears, thus causing **acquired lactose intolerance.** There are no intestinal changes.

Whipple's Disease

Malabsorptive syndrome with associated systemic symptoms secondary to infection by the gram-positive organism ***Tropheryma whippelii.***

- **Symptoms:** Typical malabsorptive symptoms along with systemic signs of infection with fever, polyarthralgias, and generalized pain. Can affect multiple organ systems.
- **Pathohistologic findings:** Distended lamina propria of the small intestine filled with distinctive **periodic acid-Schiff (PAS)-positive** macrophages with pale, foamy cytoplasm.
  - *T. whippelii* is best visualized with electron microscopy.

CLINICAL CORRELATION

In HIV-positive patients with CD4+ count < 100/μL **Whipple's-like** syndrome may develop. It is caused by ***Mycobacterium avium*** and visualized with acid-fast satin.

Other malabsorption syndromes (see Table 3-12) include but are not limited to tropical sprue, **abetalipoproteinemia,** and **intestinal lymphangiectasia.**

Diagnosis

Based on clinical findings (see Table 3-12) and biopsy (where indicated).

- In celiac sprue, **anti-gliadin,** and **anti-endomysial** antibodies have 90%–95% sensitivity and specificity, and in combination with resolution of symptoms following the elimination of gluten from the diet, one may comfortably make the diagnosis without mucosal biopsy.

Treatment

Disease-specific (see Table 3-12):

- **Celiac sprue:** Elimination of gluten-containing foods from the diet is curative in 90% of cases. Remaining patients can be treated with steroids, which typically improve symptoms.
- **Whipple's disease:** Also treated with antibiotics due to bacterial origin. Drug of choice is double-strength **trimethoprim-sulfamethoxazole** for 1 year.
- **Disaccharidase deficiency:** Avoidance of offending disaccharide or oral enzyme supplements such as lactase.

Diverticular Disease

Diverticula can be either **congenital** (involving the entire thickness of the involved segment) or **acquired** (mucosal herniation through the muscular layer). Diverticula can occur anywhere in the GI tract, including the esophagus (Zenker's diverticulum), small bowel (Meckel's diverticulum), or colon.

Diverticulosis is the condition of having diverticula, typically implied as being colonic.

Diverticulitis results when the diverticula in question become infected.

TABLE 3-12. Overview of Malabsorption Syndromes

Syndrome	Morphology	Clinical Manifestations	Treatment
Celiac sprue	▪ Gluten-sensitive enteropathy. ▪ Biopsy: Mucosal. ▪ Inflammation, villous atrophy, and crypt hyperplasia. ▪ Can be diagnosed with anti-gliadin and anti-endomysial antibodies.	Diarrhea, vitamin/mineral deficiency, **dermatitis herpetiformis** rash.	▪ Avoid gluten-containing foods such as wheat, barley, rye, and oats. ▪ Steroids (in ~ 10% of patients).
Tropical sprue	▪ Unknown occult tropical bacteria.	Diarrhea, steatorrhea, weight loss, **folate deficiency.**	**Tetracycline** for 6 months.
Whipple's disease	▪ Caused by gram-positive bacterium ***Tropheryma whippelii.*** ▪ Flat, blunt villi. ▪ Foamy **macrophages (PAS-positive)**, found in lamina propria.	Fever, polyarthralgias, weight loss, diarrhea, abdominal pain.	**Trimethoprim-sulfamethoxazole** for 1 y.
Disaccharidase deficiency	Enzyme deficiency that causes malabsorption.	Chronic diarrhea.	Avoid offending foods.
Abetalipoproteinemia	Congenital lack of apolipoprotein-B; autosomal recessive.	Steatorrhea, acanthotic erythrocytes, serum lipid abnormalities, ataxia, atypical retinitis pigmentosa.	Medium-chain triglycerides, vitamin E and fat-soluble vitamins.
Intestinal lymphangiectasia	Ectatic lymphatics; either sporadic or secondary to cardiac disease.	▪ Nausea, vomiting, intermittent diarrhea, and occasionally steatorrhea. ▪ Peripheral edema From hypoalbuminemia.	Low-fat, high-protein, medium-chain triglyceride diet.

Meckel's Diverticulum

Congenital and true diverticulum (see Figure 3-39) of the terminal ileum that results from incomplete closure of the **omphalomesenteric duct**, found in approximately 2% of the population, ~ 60 cm (2 ft) from the ileocecal valve, and normally 2 inches long. Mucosa can be ileal (50% of cases), **gastric**, pancreatic, duodenal, or colonic.

Presentation

Typically asymptomatic and discovered incidentally (patients are typically < 5 years of age).

Diagnosis

Abdominal pain can result from intussusception or volvulus.

- **Bleeding** may result from ileal peptic ulcer formation in those with gastric mucosa.
  - If gastric mucosa is present, a **Meckel's scan** may be performed by IV injection of **technetium-99** (^{99}Tc), which is taken up by the parietal cells of the ectopic gastric mucosa.



For Meckel's diverticulum, remember the rule of 2s:

2 inches long
2% of the population
2 feet from the ileocecal valve
2% are symptomatic



Meckel's diverticulum can be complicated by **Meckel's diverticulitis.** The most common presentation in children is lower GI bleeding.



FIGURE 3-39. Smooth, saccular structure of the distal small bowel consistent with a Meckel's diverticulum. Differential diagnosis: Benign ulcers of the small bowel are rare, and ulcerated malignancies are usually irregular in appearance. (Reproduced, with permission, from Chen MYM, Pope TL, Ott DJ, *Basic Radiology*, New York: McGraw-Hill, 2004: 266.)

Treatment

Once symptoms occur, surgical excision is curative.

Diverticulosis

KEY FACT

Diverticulosis is the most common cause of **painless hematochezia** in patients > 60 years old.

CLINICAL CORRELATION

Diverticulosis may lead to formation of **colonovesical fistula** that can lead to **pneumaturia** (air in the urine).

Diverticulosis is acquired (**pulsion**) multiple diverticula (see Figure 3-40) found at the origin of a mesenchymal feeder artery, and typically located in the sigmoid colon. It is thought to be secondary to increased luminal pressure caused by a **low-fiber** diet, which leads to increased colonic muscular contractions required to move stool. Incidence increases with age in Western populations, occurring in almost 50% of adults > 50 years of age.

Presentation

Typically asymptomatic and discovered incidentally on colonoscopy, abdominal CT scan, or barium enema. Massive bleeding can occur with diverticulosis secondary to vessel erosion in diverticula.

Diagnosis

As noted earlier, it is an incidental finding, unless massive bleeding occurs, in which case colonoscopy is performed (to directly visualize the diverticula), in addition to mesenteric angiography or tagged RBC scanning.

Treatment

Unless there is associated bleeding, no treatment is necessary.

- **High-fiber diets** are typically suggested in order to increase stool bulk and decrease colonic intraluminal pressure.

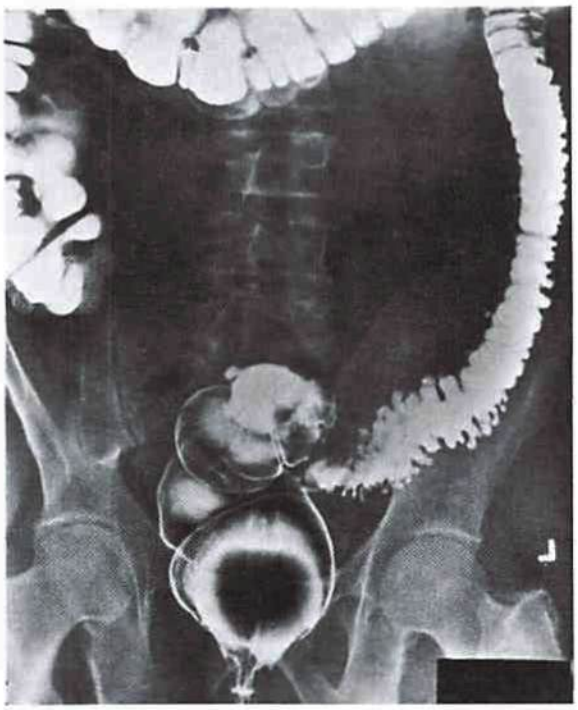


FIGURE 3-40. Diverticulosis of sigmoid colon on barium enema. (Reproduced, with permission, from Brunicardi FC, Andersen DK, Billiar TR, et al., *Schwartz's Principles of Surgery*, 8th ed, New York: McGraw-Hill, 2005: 1082.)

- Diverticular bleeding is managed with fluid repletion and transfusion as necessary. With most mild to moderate cases, bleeding resolves spontaneously (~ **80% of cases**).
- Severe cases can be treated with vessel cauterization or clipping during colonoscopic visualization.
- **Mesenteric angiography** is **both diagnostic** and **therapeutic**, as vasoconstriction and artificial blood clot formation can be induced.

Diverticulitis

Most common complication of diverticulosis, due to:

- Infection thought to be secondary to an impacted **fecalith**, resulting in lymphatic obstruction and localized ischemia, which can lead to bacterial overgrowth.
- Diverticular **rupture**, which, if contained, results in **abscess** formation. If the rupture is uncontained, **generalized peritonitis** may occur.

Presentation

Patients with diverticulitis typically present with LLQ abdominal pain, guarding, or peritoneal signs (rebound tenderness), as well as **leukocytosis**, fecal leukocytes, and fever. Constipation or obstruction may develop secondary to localized swelling.

CLINICAL CORRELATION

Typical presentation of **diverticulitis** is similar to the symptoms of **"left-sided appendicitis."**

Diagnosis

Care must be taken when obtaining imaging studies due to the risk of diverticular perforation during acute infection. Therefore, **barium enema** and **colonoscopy** are **contraindicated.**

- **Abdominal CT** scan can be used to assess for diverticular inflammation as well as pericolic abscess formation.
- An **upright abdominal plain film** should also be obtained to rule out free peritoneal air, which would suggest perforation.

Treatment

When there are no signs of perforation, treatment is bowel rest, pain management, fluid resuscitation, and **broad-spectrum antibiotics.** Surgery is required for signs of perforation as well as for drainage of large abscesses.

Intussusception

A condition that develops as a result of distal "telescoping" of a portion of the proximal bowel into a more distal one (see Figure 3-41). Most common at the **ileocecal junction.**

CLINICAL CORRELATION

Secondary causes of intussusception:
- Intestinal lymphomas
- **Meckel's diverticulum**
- Vascular malformations
- Intestinal polyps

- **Children < 2 years of age account for about 80% of cases.** It is the **most common abdominal emergency in infants** and the second most common cause of obstruction (after pyloric stenosis).
- The majority of cases are idiopathic, although there is a seasonal and clinical relationship to certain viral infections, particularly **rotavirus.**
- Remaining cases are secondary and occur when a proximal "lead point" is pulled into the distal segment by peristaltic contractions; most commonly found in adults, in which case cancer must be ruled out.

Presentation

When the proximal bowel invaginates into the distal segment, it brings its attached mesentery with it, leading to lymphatic obstruction, swelling, and decreased perfusion of the affected bowel.

- Symptoms consist of sudden onset of episodic, crampy, severe abdominal pain lasting 10–20 minutes, followed by relatively symptom-free periods. Emesis and nausea can occur during these episodes.
- The classic triad is **pain, palpable sausage-shaped mass,** and **currant-jelly stools,** although all three symptoms are not typically present at one time.



FIGURE 3-41. Gross specimen showing intussusception with overlying swelling and ischemic changes. (Image courtesy of PEIR Digital Library [http://peir.net].)

Diagnosis

Air and barium enemas are both **diagnostic and therapeutic** in most cases.

- On abdominal plain film, a filling defect in the large colon is diagnostic.
- Abdominal ultrasound can also be used to visualize the intussusception, revealing a **bull's-eye** or **coiled-spring** pattern due to invagination of the proximal segment.

Treatment

As mentioned, nonsurgical means are attempted first (**air or barium enema**). Surgery is indicated if air or barium enema fails or if perforation occurs.

Hirschsprung's Disease (Congenital Megacolon)

Hirschsprung's disease (HD) is characterized by **complete functional obstruction** of the large bowel due to the **absence of ganglion cells** of both the submucosal and myenteric neural plexuses.

- Aganglionic bowel **always** involves the **anus** and then progresses proximally to varying degrees (the most severe disease involves the entire colon and even some small intestine).
- Obstruction leads to the characteristic **dilation** of the bowel proximal to the aganglionic segment, hence, the name **congenital megacolon.**
- Several **genetic mutations** have been associated with HD, the most common of which is the *RET* proto-oncogene.
- HD has also been associated with Down's syndrome, Waardenburg's syndrome, cardiac defects, and several other congenital conditions. HD occurs in about 1:5000 live births, with a male:female ratio of 3:1 or 4:1.

Presentation

Typically presents in a newborn with failure to pass meconium within the first 48 hours of life. Other symptoms of bowel obstruction can be present, such as bilious vomiting and abdominal distention. In less severe cases, HD can present as chronic constipation in an adolescent or young adult.

Diagnosis

- Rectal biopsy is considered the gold standard for diagnosis and will reveal the absence of ganglion cells in the rectal tissue.
- Barium enema can suggest the diagnosis and will show severe dilation of the proximal colon that abruptly narrows into the aganglionic distal colon.

Treatment

Surgical correction. The aganglionic section is resected and the normal bowel is connected to the anus.

KEY FACT

In HD, the aganglionic section of bowel corresponds to the narrowed narrowing segment, while the dilated portion of bowel is structurally normal.

KEY FACT

In achalasia, it is the dilated portion of esophagus that lacks ganglia, while the narrowed portion is structurally normal.

? CLINICAL CORRELATION

Early differential diagnosis of **HD** includes **CF,** which may present similarly.

INFLAMMATORY DISEASES OF THE COLON

By definition, ***colitis*** is an inflammation of the colon. Based on the etiology, there are several types of colitis, of which we address the most common.

Crohn's Disease (CD) and Ulcerative Colitis (UC)

These are two major idiopathic types of IBDs (see Figures 3-42 and 3-43).

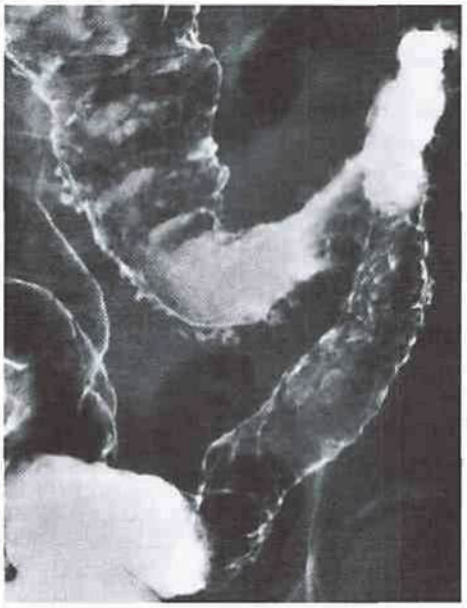


FIGURE 3-42. Crohn's disease. Segmental CD of the transverse and descending portions of the colon, showing multiple deep ulcers projecting from the margins of the affected colon, and small aphthoid ulcers appearing like erosions seen in the upper GI tract. (Reproduced, with permission, from Chen MYM, Pope TL, Ott DJ, *Basic Radiology*, New York: McGraw-Hill, 2004: 275.)

MNEMONIC

For **Crohn's,** think of a **fat granny** and an old **crone skip**ping down a **cobblestone** road away from the **wreck** (rectal sparing).

CLINICAL CORRELATION

IBDs should be differentiated from:

- Irritable bowel syndrome
- Radiation colitis
- Ischemic colitis
- A variety of infectious processes
- Colitis related to medications

Presentation

UC and CD share many features resulting from bowel inflammation, including diarrhea, pain, fever, and blood loss, but differ in important ways, as listed in Table 3-13.

Diagnosis

Characteristic history coupled with a typical radiographic (see Figure 3-42 for CD) and endoscopic (gross) appearance of the mucosa (see Figure 3-43 for UC), in addition to confirmatory histology seen on colonic biopsy.

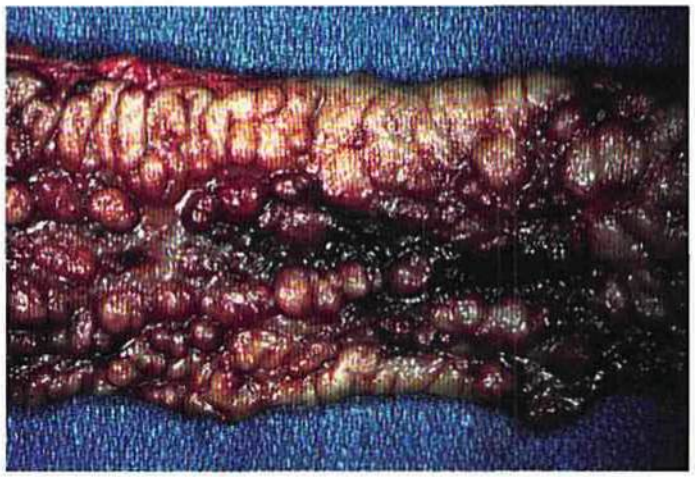


FIGURE 3-43. Ulcerative colitis. Gross image with pseudopolyposis. (Image courtesy of PEIR Digital Library [http://peir.net].)

TABLE 3-13. Clinical and Pathologic Features of CD and UC

	CD	UC
Possible etiology	Infectious.	Autoimmune.
Location	May involve any portion of the GI tract, usually the terminal ileum and colon; **skip lesions,** with **rectal** sparing.	**Colitis** is colonic inflammation; **continuous lesions,** always with rectal involvement.
Gross morphology	Transmural inflammation; **cobblestone-like** mucosa, **creeping fat,** bowel wall thickening ("string sign" on barium swallow), linear ulcers, fissures, fistulas.	Mucosal and submucosal inflammation only; friable mucosal pseudopoylps with freely hanging mesentery.
Microscopic morphology	Noncaseating **granulomas** and lymphoid aggregates.	Crypt abscesses and ulcers, bleeding, **no granulomas.**
Complications	Strictures, fistulas, perianal disease, malabsorption, nutritional depletion.	Severe stenosis, toxic megacolon, **colorectal carcinoma.**
Extraintestinal manifestations	Migratory polyarthritis, erythema nodosum, ankylosing spondylitis, uveitis, immunologic disorders.	Pyoderma gangrenosum, primary sclerosing cholangitis.

Treatment

The medical treatment for both IBDs is similar and includes **anti-inflammatory** (sulfasalazine for milder forms; corticosteroids and azathioprine for more severe cases), **antidiarrheal,** and **antibiotic** medications.

Prognosis

Surgical therapy (**colectomy**):

- In patients with uncontrolled UC, colectomy is **curative.**
- In patients with CD, surgery is **not curative,** but is required to manage complications in 70% of patients.
- **UC predisposes to carcinoma of the colon,** most commonly **occurring after > 10 years.**

FLASH FORWARD

- **Sulfasalazine** is not absorbed by the small intestine.
- It is hydrolyzed by colon flora into **5-aminosalicylate acid (5-ASA)** (mesalazine) and **sulfapyridine.**
- 5-ASA acts as a local anti-inflammatory agent in the colon.

Pseudomembranous Colitis

Pseudomembranous colitis is an acute inflammation of the colon, precipitated by a course of antibiotics (classically, ampicillin, clindamycin, or a cephalosporin) that clear the normal colonic bacterial flora (*E. coli* and *Bacteroides fragilis*), thus enabling overgrowth of *Clostridium difficile*.

FLASH BACK

C. difficile is a gram-positive, spore-forming anaerobic rod. Antibiotic therapy drastically decreases protective flora, allowing *C. difficile* to become pathogenic.

Presentation

Symptoms are due to the *C. difficile* toxins. A and B toxins attack the colonic mucosa, leading to hypermotility, inflammation, and increased capillary permeability.

- Typical symptoms include frequent watery diarrhea, abdominal pain or cramping, and fever. It can also be associated with occult colonic bleeding.
- In severe cases, the colonic mucosa becomes covered with yellow or gray exudates, hence the term **pseudomembranous colitis** (see Figure 3-44). This can lead to toxic megacolon, volvulus, or colonic perforation, all of which can be life-threatening.



FIGURE 3-44. Pseudomembranous colitis. (Image courtesy of PEIR Digital Library [http://peir.net].)

Diagnosis

A stool sample is tested for the A and B toxins of *C. difficile*.

- Colonoscopy is rarely indicated, but if done, demonstrates confluent patches of yellow or gray exudates obscuring the normal colonic mucosa.

Treatment

The first step in treating pseudomembranous colitis is stopping the inciting antibiotic.

- **Antidiarrheal agents** such as loperamide are **contraindicated**, as they will prolong production of toxins in the colon, thus worsening the condition.
- Supportive therapy is typically sufficient in the immunocompetent adult.
- In patients with more severe illness or with multiple medical problems, *C. difficile* can be treated with metronidazole (first-line) or oral vancomycin.

Infectious Colitis

FLASH BACK

Most common microorganisms involved in infectious diarrhea:

- *E. coli*
- *V. cholerae*
- *Salmonella*
- *Shigella*
- *Campylobacter jejuni*
- *Vibrio parahaemolyticus*
- *Yersinia enterocolitica*
- Rotavirus
- Norwalk virus
- *Cryptosporidium*
- *Giardia lamblia*

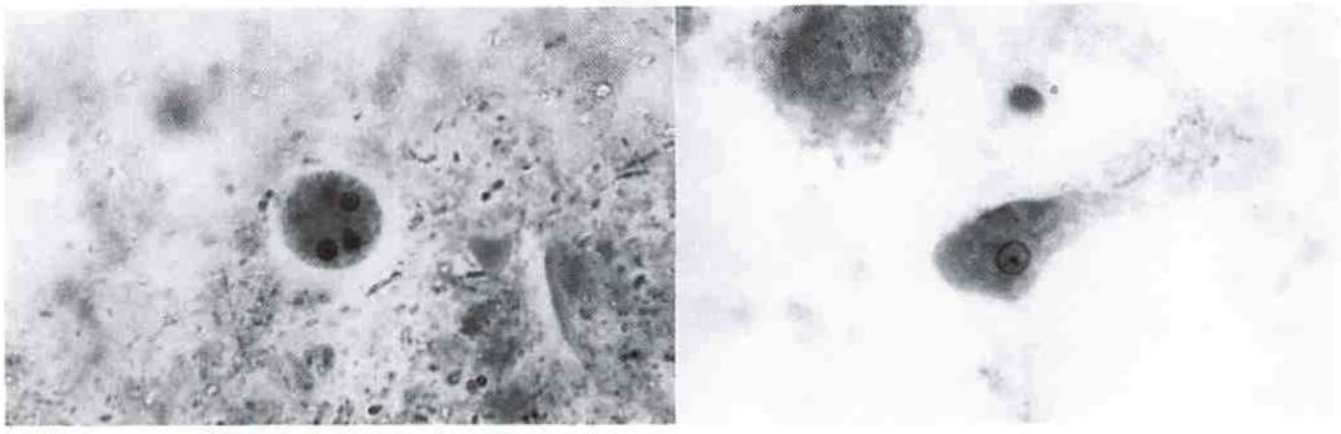
Infectious causes of colitis can be viral, bacterial, or parasitic. Patients with infectious colitis typically present with severe diarrhea, fever, leukocytosis, and abdominal pain. Clues in the history may include travel, recent antibiotic use, specific food consumption, and immunodeficiency.

The most commonly implicated pathogens include:

- ***Entamoeba histolytica*** (see Figure 3-45): The clinical presentation of amebic colitis ranges from being asymptomatic to causing severe bloody diarrhea, extraintestinal disease such as amebic liver abscesses, and finally bowel necrosis, perforation, and fulminant peritonitis.
- ***Vibrio cholerae***: This gram-negative bacterium produces a toxin that causes watery diarrhea with profound loss of fluid and electrolytes. The dehydration caused by cholera can be deadly in a matter of days without adequate fluid and electrolyte resuscitation.

Treatment

Depends on the underlying (suspected) microorganism. If bacterial/parasitic etiology is implicated, appropriate antimicrobial or antiparasitic therapy is needed. Maintain adequate supportive care at all times.



A B

FIGURE 3-45. *Entamoeba histolytica* cyst (A) showing three of the four nuclei, and trophozoite (B) demonstrating a single nucleus with a central, dot-like nucleolus. (Reproduced, with permission, from Fauci AS, Braunwald E, Kasper DL, et al., eds. *Harrison's Principles of Internal Medicine*, 17th ed, New York: McGraw-Hill, 2008; 1215.)

TUMORS OF THE COLON

Benign Polyps

Polyps in the colon are extremely common after age 40 and can be precursors to colorectal cancer.

- **Hyperplastic polyps** are the most common type of benign polyp.
- **Other types** include submucosal polyps, inflammatory pseudopolyps, and hamartomatous polyps. These benign polyps have a very low rate of malignant conversion except in the hereditary polyposes.

Adenomatous Polyps

By definition, adenomatous polyps are dysplastic and therefore have malignant potential. There are three subtypes:

- **Tubular** adenomas are the most common of the three, and are so named because their neoplastic glands are rounded or tubular.
- **Villous** adenomas have the **highest rate of malignant conversion.** Histologically, they have a cauliflower-like appearance with finger-like villi extending down into the center of the polyp.
- **Tubulovillous** polyps (see Figure 3-46) are so named because they have characteristics of both tubular and villous adenomas; they have an intermediate rate of malignant conversion.

Multiple Polyposis Syndromes

There are several genetic disorders that cause multiple colonic polyps, usually at young ages. Polyps and tumors typically arise in the proximal (right-sided) colon.

Familial Adenomatous Polyposis (FAP)

Autosomal **dominant** genetic disorder caused by a mutation in the adenomatous polyposis coli (APC) gene. Those affected have numerous precancerous and cancerous colon polyps (see Figure 3-47) in the second or third decade of life; the diagnosis is clinched if more than 100 colorectal polyps are found. Virtually 100% of affected patients develop colorectal cancer. Prophy-

CLINICAL CORRELATION

Extraintestinal tumors commonly develop in conjunction with these disorders.

CLINICAL CORRELATION

Commonly affected sites include the endometrium (endometrial carcinoma), ovary, stomach, bowel, pancreas, hepatobiliary system, urinary system, and prostate.



FIGURE 3-46. Tubulovillous adenoma. Histological image of a pedunculated tubular adenoma with some features of villous adenoma (tubulovillous adenoma). (Image courtesy of PEIR Digital Library [http://peir.net].)

lactic total colectomy is therefore indicated even during childhood or early adulthood.

- FAP is also associated with **periampullary tumors.** This is the second leading cause of death in patients with FAP.

GARDNER'S SYNDROME

Autosomal **dominant** genetic disorder characterized by multiple adenomatous colon polyps in conjunction with other extraintestinal tumors, including osteomas, hepatoblastomas, papillary thyroid carcinoma, and periampullary adenomas.

TURCOT'S SYNDROME

Autosomal **recessive** disorder that causes colonic polyps and tumors of the CNS, especially glioblastoma multiforme and medulloblastoma.

HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC)

Autosomal **dominant** disorder that causes colorectal adenomas and colorectal cancer. A mutation in a **DNA mismatch repair gene** (*hMLH1* **or** *hMSH* 2)

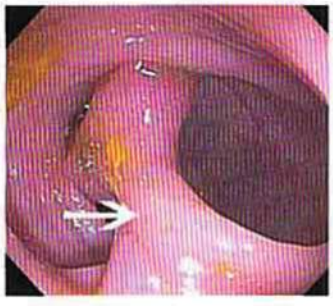


FIGURE 3-47. Pedunculated colon polyp on a thick stalk covered with normal mucosa (arrow). (Reproduced, with permission, from Fauci AS, Kasper DL, Braunwald E, et al, eds. *Harrison's Principles of Internal Medicine*, 17th ed, New York: McGraw-Hill, 2008. Figure 285-5)

is thought to be the cause of the disease. HNPCC has also been classified as part of Lynch I or Lynch II syndrome. Lynch II syndrome is also associated with extracolonic tumors (endometrium, ovary, and pancreas).

Peutz-Jeghers' Syndrome

Autosomal dominant disorder characterized by a combination of hamartomatous colon polyps and **mucocutaneous hyperpigmented lesions** on the lips (see Figure 3-48), oral mucosa, hands, and genitals. The colon polyps rarely become cancerous, but they can cause symptoms such as obstruction, pain, and bleeding. Those affected have a higher likelihood of cancer in the stomach, breast, and ovaries.

Colorectal Cancer

Histologically, colorectal cancer is **adenocarcinoma of the large intestine and/or rectum.** It is the third most common cancer as well as the second leading cause of cancer-related death in both men and women in the United States.

- **Risk factors** include advanced age, family history, low-fiber diet, villous adenomas, IBD (especially UC), FAP, Peutz-Jeghers juvenile nonpolyposis, and HNPCC. Screening should start at age 50 with colonoscopy, barium enema, or flexible sigmoidoscopy plus fecal occult blood testing.
- Colon cancer typically arises from dysplastic adenomas in the colon. Research shows that over time, underlying genetic mutations along with environmental influences **(two-hit hypothesis)** lead to the stepwise conversion of normal colonic epithelium into dysplastic adenomas, and finally, to malignant adenocarcinoma (**adenoma-carcinoma sequence**; see Figure 3-49).
- The most common mutations are in the *APC* gene, which occur **early** in the development of colon cancer, and in the *p53* gene, which occur **later.** Many other gene mutations, including the *K-RAS* gene, have been implicated and occur at various stages in the development of cancer.

KEY FACT

The *K-RAS* gene encodes a signal transduction molecule that oscillates between an activated GTP and an inactivated GDP.

KEY FACT

Mutated *RAS* remains in an activated state, continuously delivering mitotic signals, thus preventing apoptosis.

Presentation

Colon cancer typically occurs in adults over 50.

- It can present with changes in stools (i.e., melena, hematochezia, pencil-thin–caliber stools), abdominal discomfort, or constitutional symptoms such as weight loss. Unexplained anemia in men and postmenopausal women is a relatively common finding.



FIGURE 3-48. Peutz-Jehgers' syndrome. (Image courtesy of Uniformed Services University of the Health Sciences.)

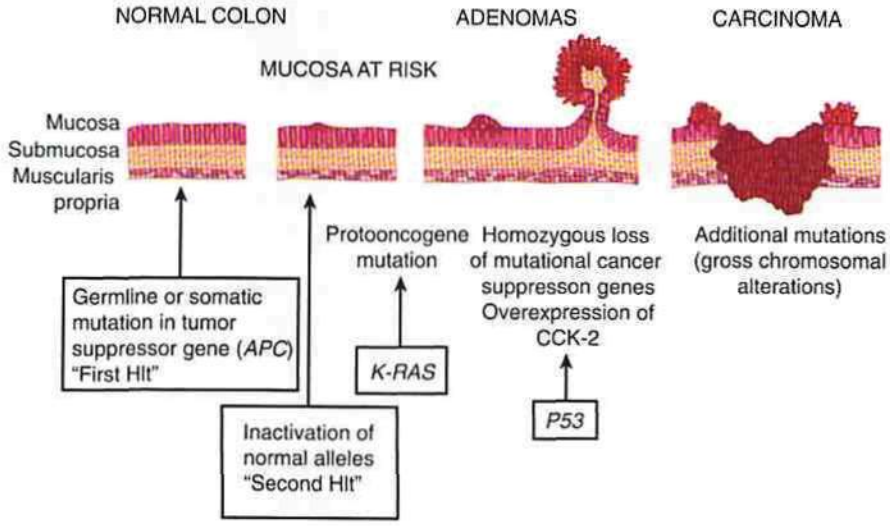


FIGURE 3-49. Adenoma-carcinoma sequence. The development of carcinoma from adenomatous lesions is referred to as the adenoma-carcinoma sequence.

- **Left-sided (sigmoid) colon cancer:**
  - **Early** symptoms of **obstruction** (the left side has a narrower lumen).
  - Tumors produce a "**napkin-ring**" or "**apple-core**" constriction (encircling annular growth; see Figure 3-50).
  - Stool is **solid.**
- **Right-sided colon cancer:**
  - **Anemia,** weight loss, and abdominal **pain.**
  - Tumors look like **cauliflower** (polypoid or fungating appearance).
  - Stool is watery in the right colon; thus, obstruction seldom occurs.

Diagnosis

Colonoscopy with tissue biopsy revealing adenocarcinoma is the gold standard for diagnosis. Once the diagnosis is made, CT scans are done to look for metastases.

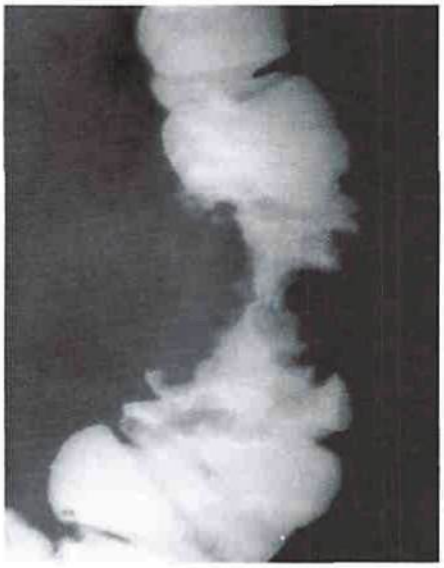


FIGURE 3-50. Annular, constricting adenocarcinoma of the descending colon. This radiographic appearance is referred to as an "apple-core" lesion and is always highly suggestive of malignancy. (Reproduced, with permission, from Kasper DL, Braunwald E, Fauci AS, eds, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 530.)

- **Screening** is recommended beginning at age 50; screening tests include colonoscopy, fecal occult blood testing, flexible sigmoidoscopy, barium enema, and digital rectal exam.
- **Carcinoembryonic antigen (CEA)** is not recommended as a diagnostic serum marker for colon cancer; however, it can be very useful in evaluating the success of surgical resection, as well as in monitoring the growth and/or recurrence of the cancer.

Treatment

Surgical resection and chemotherapy (usually involving fluorouracil) are the most common treatments.

- Colon cancer can **metastasize hematogenously** as well as through the **lymphatics.**
- The most common sites of **metastasis** are the regional lymph nodes, **liver,** lungs, and peritoneum; other possible sites for metastases are the bones and brain.

Prognosis

Depends on the stage of the tumor at diagnosis. Favorable when the cancer is detected early, before metastasis has occurred. Once widespread, the 5-year survival rate drops to < 10%.

CLINICAL CORRELATION

CEA can be elevated in other conditions:

Malignant: Cancers of the pancreas, stomach, breast, lung, and certain types of thyroid and ovarian cancers.

Benign: Smoking, infections, IBD, pancreatitis, cirrhosis of the liver, and some benign tumors of organs listed above.

Other: Chemotherapy and radiation therapy may lead to temporary elevation of CEA (massive death of tumor cells releases CEA into the circulation).

APPENDICITIS

Appendicitis is the most common indication for emergency abdominal surgery in children, but it can occur in all age groups, with peak ages 15–30 years.

Presentation

Classic presentation is fever and periumbilical abdominal pain, later localizing to the RLQ (**McBurney's point**), accompanied by signs of peritoneal irritation. Anorexia, vomiting, constipation, and diarrhea may also be present.

FLASH BACK

McBurney's point is located two-thirds of the distance from the umbilicus to the anterior superior iliac spine.

Diagnosis

Leukocytosis, pyuria, and fecal leukocytes are the most common laboratory findings.

- Abdominal X-ray shows a radiopaque fecalith (fecal material impacted into the appendix) in two-thirds of cases.
- Abdominal CT is generally diagnostic and should be performed in equivocal cases.
- Differential diagnosis includes diverticulitis in the elderly and in ectopic pregnancy (should be ruled out with β-human chorionic gonadotropin testing in all premenopausal females).

Treatment

Surgical appendectomy is necessary and curative. There is a 40% rate of perforation in the pediatric population, but the mortality rate is < 1%.

ABDOMINAL HERNIAS

Hernias are abnormal protrusions of the abdominal contents through a defect in the abdominal wall.

The **hernial mass** consists of three parts: covering tissues (formed by layers of the abdominal wall), a peritoneal sac, and any structure (including viscera) contained within the abdominal cavity.

KEY FACT

- Groin hernias (direct inguinal, indirect inguinal, and femoral) account for the majority (75%) of cases.
- Incisional and ventral hernias are less common (10%).
- Umbilical hernias (3%) are more prevalent in infants.
- Other rare hernias (e.g., spigelian, Petit's, and internal) account for the remainder.

Most hernias are **congenital** (e.g., indirect inguinal hernias due to fascial weakness), while others are **iatrogenic** (e.g., incisional hernias due to a fascial defect created by surgical incision). Causes of the most common abdominal hernias, in order of prevalence, are shown in Table 3-14.

Hernias are described as reducible, irreducible, or strangulated.

- **Reducible:** Most common type, usually painless. The abdominal contents can be easily returned to the abdomen.
- **Irreducible (incarcerated):** Difficult to return the contents to the abdominal cavity. Can become painful if bowel is obstructed or incarcerated.
- **Strangulated:** The entrapped organ (usually bowel, sometimes fat) becomes incarcerated in the fascial defect, resulting in compromised blood supply. Strangulated hernias are intensely painful and very dangerous due to bowel obstruction and possible necrosis. They require immediate surgical repair.

Presentation

Patients classically present as children or young adults, but hernias can present at any age and may be aggravated or uncovered by comorbid medical conditions that cause increased intra-abdominal pressure in older patients (i.e., chronic cough, COPD, constipation).

KEY FACT

Hesselbach's (inguinal) triangle: A site of direct inguinal hernias:
- Rectus abdominis muscle (medial)
- Inguinal ligament (inferior)
- Inferior epigastric blood vessels (superior and lateral)

- **Inguinal hernias:** Most common type; more often seen in **men.** Clinically, direct and indirect hernias present identically and are treated in the same way. Patients usually complain of a painless bulge in the inguinal region that is exacerbated by increased intra-abdominal pressure (i.e., coughing, straining with defecation, lifting weight). Patients may also have a feeling of heaviness in the groin.
- **Femoral hernias:** More often seen in **women.** Patients frequently present with a palpable lump medial to the femoral pulse and inferior to the ingui-

TABLE 3-14. Causes of the Most Common Abdominal Hernias

Hernia Type	Cause	Location
Indirect inguinal hernia	Congenital weakness in the fascial margin of the internal inguinal ring (patent processus vaginalis).	Originate lateral to the inferior epigastric vessels.
Direct inguinal hernia	Congenital weakness in the fascia of the inguinal canal floor.	Originate medial to the inferior epigastric vessels (above and medial to the pubic tubercle).
Femoral hernia	Weakness of the femoral septum, allowing protrusion of the hernial sac through the femoral canal within the femoral sheath.	Originate below and lateral to the pubic tubercle.
Umbilical	Congenital (e.g., infants) or acquired (e.g., multiparous women) abnormality in the musculature around the umbilical cord.	Originate at the umbilicus.
Incisional	Acquired as a postoperative complication.	Originate at surgical incision sites.

nal ligament. These hernias have a tendency to become incarcerated or strangulated because of the relatively small area of the femoral ring and the presence of unyielding anatomic structures (e.g., sharp free edge of the lacunar ligament). Consequently, these hernias can be painful and require prompt surgical repair.

- **Umbilical hernias:** Often present in **infants** or **children** due to congenital defects in the abdominal wall at the umbilicus. In adults, umbilical hernias are more common in multiparous women and patients with comorbid medical conditions that cause chronically increased abdominal pressure (i.e., chronic cough, COPD, ascites). Patients usually complain of a bulge at the umbilicus that worsens on Valsalva maneuver. Pain may be present if bowel becomes incarcerated or strangulated. Severe pain and erythema of the skin suggest necrosis of underlying bowel, and warrants immediate surgical repair.

MNEMONIC

Both *indirect* and *direct* hernias occur in the inguinal canal.
INdirect hernias are **IN** the **IN**ternal ring and spermatic cord and commonly occur in **IN**fants.

Diagnosis

Based on clinical symptoms.

- Physical exam:
  - **Inguinal** hernias in **men** are palpated by pushing a finger into the skin of the scrotum and directing it laterally and upward toward the internal inguinal ring. **Valsalva maneuver** (coughing) pushes the hernia against the examiner's finger. In **women**, the hernia can be palpated directly over the internal inguinal ring on Valsalva maneuver.
  - **Femoral** hernias can often be palpated medial to the femoral pulse and inferior to the inguinal ring.
- CT scan or ultrasound may be necessary with patients who have hernias that are not easily palpable (i.e., obese patients).

Treatment

Surgical repair (herniorraphy).

HEPATOBILIARY SYSTEM

Jaundice

Patients with jaundice often present with yellowed skin or sclera that represents an underlying increase in serum bilirubin (see Table 3-15).

- **Physiologic jaundice:** Extremely common (50% of newborns). A condition **in neonates** that results from the relative deficiency in glucuronyl transferase in the immature liver in newborns.
  - **Hemolysis** resulting from mild trauma during the birth process can exacerbate the condition by increasing bilirubin production.
- **Adult jaundice:** A pathologic process due to overproduction (e.g., hemolysis) or impaired excretion (e.g., bile duct obstruction, hepatocellular dysfunction) of bilirubin.

Presentation

Scleral icterus typically appears first, generally at serum bilirubin leves > 3 mg/dL. Jaundice is seen at even higher levels of serum bilirubin.

- **Newborns:** Jaundice present **at birth** is **pathologic.** In contrast, **physiologic jaundice** of the newborn is clinically benign and occurs **48–72 hours following birth.** Bilirubin levels rise at < 5 mg/dL/day and peak at < 15 mg/dL. Direct bilirubin comprises < 10% of the total.

CLINICAL CORRELATION

By far, the most common cause of jaundice is choledocholithiasis.

TABLE 3-15. Jaundice: Underlying Etiologies

Jaundice	Diseases	Serum Bilirubin	Urine Bilirubin	Urine Urobilinogen
Conjugated	**Hepatocellular disease:** ▪ Dubin-Johnson's syndrome: Inherited defect in liver excretion of bilirubin leads to a glossy black liver ▪ Rotor syndrome: Less severe without a black liver **Obstruction of the bile duct by:** ▪ Gallstones ▪ Tumors ▪ Primary sclerosing cholangitis (PSC) ▪ Parasites	↑ Direct bilirubin (>15%)	↑	Normal/≠
Unconjugated	**Hemolytic diseases:** ▪ Sickle cell ▪ Glucose-6-phosphate dehydrogenase deficiency ▪ Spherocytosis ▪ Microangiopathic hemolytic anemia ▪ Paroxysmal nocturnal hemoglobinuria ▪ ABO/Rh isoimmunization ▪ Autoimmune hemolytic anemia (warm and cold) **Inherited hepatocellular diseases:** ▪ Crigler-Najjar type 1: Absent UDP-glucuronyl transferase ▪ Crigler-Najjar type 2: Less severe and responds to phenobarbital, which induces hepatic enzymes, including UDP-glucuronyl transferase ▪ Gilbert's syndrome: Mild rise in UDP glucuronyl transferase, which causes asymptomatic rise in indirect bilirubin, associated with stress; common, affecting about 5% of the population **Acquired hepatocellular disease:** ▪ Cirrhosis ▪ Hepatitis ▪ Drugs (i.e., steroids, rifampin, probenecid, ribavirin) ▪ Liver failure (i.e., sepsis)	↑ Indirect bilirubin	Absent (acholuria)	↑ (from heme metabolism)

CLINICAL CORRELATION

Other common clinical entities are tumors (especially pancreatic) and liver failure.

Diagnosis

The **most important step** in diagnosis is determining if the jaundice is secondary to conjugated (direct) or unconjugated (indirect) hyperbilirubinemia (see Figure 3-51).

- **Direct** hyperbilirubinemia is always pathologic.
- **Indirect** hyperbilirubinemia may be physiologic or pathologic.

Treatment

Address the underlying condition. Physiologic jaundice of the newborn typically resolves with normal maturation and UV light exposure within 1–2 weeks.

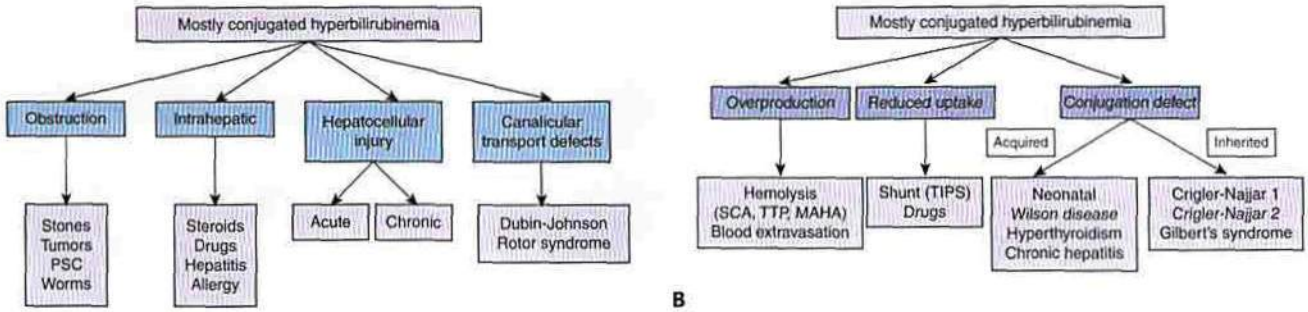


FIGURE 3-51. Differential diagnosis for elevation of (A) direct and (B) indirect bilirubin. PSC = primary sclerosing cholangitis; MAHA = microangiopathic hemolytic anemia; TIPS = transjugular intrahepatic portosystemic shunt; TTP = thrombotic thrombocytopenic purpura; SCA = sickle cell anemia.

Prognosis

Easily treatable etiologies have a much better prognosis than do malignant obstruction or hepatocellular etiologies.

Hereditary Hyperbilirubinemias

Rare conditions can be differentiated by the predominant form of bile acids (conjugated or unconjugated) present in the bloodstream.

Hereditary Causes of Direct (Conjugated) Hyperbilirubinemia

Dubin-Johnson's Syndrome

Rare inherited (**autosomal recessive**) condition caused by impaired intrahepatic bilirubin secretion.

- The defect is due to the absence of the canilicular protein **multidrug-resistant protein 2 (MRP2)**, which is responsible for transport of bilirubin glucuronides and other anions into the bile.
- Grossly, the **liver** appears **black.** Functionally, the liver is normal.

Presentation

Mostly asymptomatic, but may present with chronic or recurring jaundice of varying intensity.

Diagnosis

- Elevated serum direct bilirubin
- Normal CBC
- Normal liver enzymes
- Grossly black liver on biopsy

Treatment

No treatment is usually necessary. Individuals with this disorder have a normal life expectancy.

- If the bilirubin rises to levels requiring treatment, patients respond well to **phenobarbital,** which reduces jaundice by inducing hypertrophy of the hepatocellular ER, thus improving bilirubin conjugation.

Rotor's Syndrome

Similar to Dubin-Johnson's syndrome, caused by multiple defects in both hepatocellular uptake and secretion of bilirubin. Grossly, however, the **liver appears normal.** Patients respond well to **phenobarbital.**

Hereditary Causes of Indirect (Unconjugated) Hyperbilirubinemia

Gilbert's Syndrome

Benign inherited condition causing mild, intermittent indirect hyperbilirubinemia.

- Caused by transient reduction in hepatic glucuronyl transferase activity to about one-third normal levels.

Presentation

Usually an incidental finding in an otherwise healthy adolescent or young adult male (male:female predominance 2–7:1); manifests as **mild jaundice** during **periods of stress,** such as concurrent illness, strenuous exercise, or fasting.

Diagnosis

- Elevated serum indirect bilirubin (usually 2–3 times normal, almost always < 6 mg/dL).
- Normal CBC.
- Normal liver enzymes.

Treatment

No treatment necessary; reassurance only.

Crigler-Najjar's Syndrome (Type 1)

Rare genetic syndrome (autosomal recessive). Type 1 is the severe form and is caused by a **complete lack of hepatic glucuronyl transferase, the enzyme responsible for conjugation of indirect to direct bilirubin.** On gross inspection, the liver appears normal.

Presentation

Suspect in **neonates** presenting with severe **jaundice at birth.** Due to the complete lack of glucuronyl transferase, bile is colorless and contains only traces of unconjugated bilirubin. Prior to the availability of phototherapy, newborns would develop **kernicterus** (bilirubin encephalopathy).

Diagnosis

Severe jaundice and icterus in a newborn with severely elevated serum indirect bilirubin (**> 30 times normal values**).

Treatment

Aggressive treatment with phototherapy and exchange transfusions in the immediate neonatal period.

- Heme oxygenase inhibitors and cholestyramine.
- Liver transplant prior to onset of brain damage (neurologic symptoms).
- Patients **do not** respond to **phenobarbital.**
- Fatal within 18 months after birth if untreated (kernicterus).

Crigler-Najjar's Syndrome (Type 2)

Less severe than type 1, a nonfatal disorder caused by a **partial lack of hepatic glucuronyl transferase.** As with type 1, the liver is morphologically normal.

Presentation

Suspect in **neonates** presenting with severe **jaundice at birth.** Babies have strikingly yellow skin due to high levels of indirect bilirubin.

Diagnosis

Severe jaundice in a newborn and severely elevated serum indirect bilirubin.

Treatment

Phototherapy; patients respond to phenobarbital.

Prognosis

Can lead to neurologic damage due to kernicterus if untreated. Excellent prognosis if treated; patients will develop normally.

Alcoholic Hepatitis

Alcoholic hepatitis is due to reversible inflammatory liver damage caused by a high level of alcohol consumption over time. The pathophysiology is poorly understood, and it is thought that genetic and environmental factors play an important role.

- Direct toxicity from ethanol and its metabolites in addition to oxidative damage disrupt the function of cell and mitochondrial membranes, thus leading to lipid accumulation.

Presentation

Can be asymptomatic in its mildest form, or can present with fulminant hepatic failure and death in its most severe form.

- **Classic presentation:** Nausea, malaise, tachycardia, and low-grade fever in an individual with a history of heavy alcohol use.
- **Patients with concomitant hepatic failure or portal hypertension:** Ascites, significant hematemesis from ruptured esophageal varices, or evidence of encephalopathy, such as asterixis and altered mental status. RUQ tenderness and hepatomegaly may be noted on physical exam.

MNEMONIC

A Scotch and Tonic:

Alcoholic hepatitis: **AST** >> ALT
Viral hepatitis: **AST** << ALT

Diagnosis

Clinical diagnosis can be made based on presentation and history of alcohol abuse.

- **Lab tests** reveal elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in a ratio of 2:1, elevated alkaline phosphatase (ALP), and prolonged prothrombin time (PT).
- **Tissue exam** (see Figure 3-52): Steatosis, neutrophilic infiltrate, centrilobular ballooning necrosis of hepatocytes, and Mallory's hyaline inclusion bodies.

KEY FACT

A mildly elevated AST may be the only laboratory abnormality in mild cases.

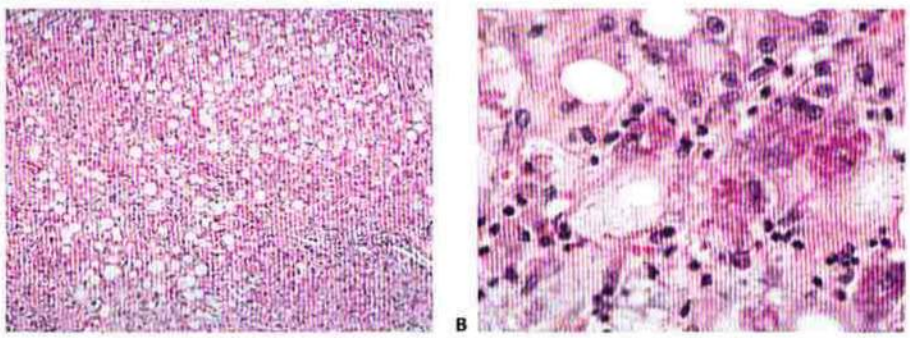


FIGURE 3-52. Microscopic features of alcoholic hepatitis. (A) Fatty change and cirrhosis inflammation characterized by focal microvesicular steatosis, Mallory bodies, and scattered PMNs permeating the parenchyma. (B) High-power microscopic view of fatty change Mallory bodies and neutrophils. (Images courtesy of PEIR Digital Library [http://peir.net].)

Treatment

Alcoholic hepatitis is completely reversible if the patient is able to achieve abstinence from alcohol.

- **Immediate treatment** should include nutritional support with **thiamine** and **folate**, as well as close monitoring for alcohol withdrawal, which can be fatal if left untreated.
- **Vitamin K** should be given to reverse coagulopathy.

Prognosis

If alcohol abuse continues, the patient risks cirrhosis, which carries a much poorer prognosis.

Reye's Syndrome

Reye's syndrome is a rare childhood hepatoencephalopathy. The pathogenesis is thought to be damage to mitochondria caused by **salicylate (aspirin)** metabolites or some other toxin in the milieu of a viral infection or underlying mitochondrial polymorphism.

- Mitochondrial dysfunction leads to elevation of short-chain fatty acids and hyperammonemia as well as cerebral edema.

KEY FACT

AST is located in the mitochondria; thus, mitochondrial damage results in elevated AST (Reye's syndrome and alcoholic hepatitis).

Presentation

Vomiting, lethargy, drowsiness, and progressive stupor, usually preceeded by upper respiratory infection (e.g., influenza A or B or varicella) combined with **salicylate** use. Signs of increased intracranial pressure, such as hyperpnea, irregular respirations, and sluggish pupils, may also be present.

Diagnosis

- Lab findings reflect liver damage and include:
  - Elevated **AST**
  - **Hyperammonemia**
  - Normal or slightly elevated **bilirubin**
  - Prolonged **PT**
- **Histology** of the liver shows diffuse microvesicular steatosis (nucleus is **not** dislocated) with **large, pleomorphic mitochondria.**

Treatment

Generally supportive. If cerebral edema is controlled, the liver usually is able to regenerate. **Intracranial pressure** is managed with hyperventilation, mannitol, and barbiturates.

Prognosis

At least 70% of patients survive, and the prognosis is related to the depth of coma and peak ammonia levels. Patients should be screened for fatty acid metabolism defects and should not be given aspirin.

Cirrhosis and Portal Hypertension

Cirrhosis is an **irreversible scarring** of the liver that occurs after years of chronic insult. In essence, cirrhosis is **chronic liver damage,** characterized by complete disarray of the hepatic cytoarchitecture, with progressive scarring (generalized fibrosis) and typical "regenerative" nodule formation. Morphologically (see Figures 3-53 and 3-54), it can be divided into:

- **Micronodular cirrhosis:** Nodules < 3 mm, uniform in size.

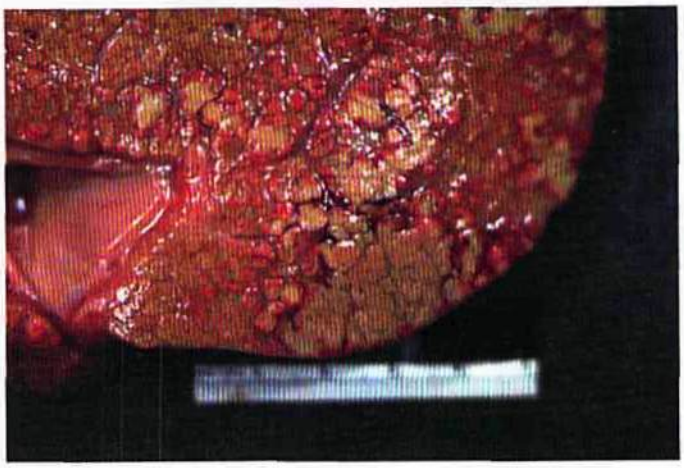


FIGURE 3-53. End-stage cirrhosis with lobular necrosis. (Image courtesy of PEIR Digital Library [http://peir.net].)

- **Macronodular cirrhosis:** Nodules > 3 mm, with increased risk of hepatocellular carcinoma (HCC), usually due to significant liver injury leading to hepatic necrosis (postinfectious or drug-induced).
- **Mixed: Macromicronodular** form.

There are many etiologic agents involved in the development of cirrhosis (see Table 3-16). They are generally divided into four major groups:

- Infectious.
- Inherited/metabolic disorders.
- Drugs/toxins affecting the liver.
- Other causes: Underlying primary diseases that ultimately affect the liver.

Cirrhosis is a major risk factor for the development of HCC.

Alcoholic Cirrhosis

Alcoholism is the most common cause of cirrhosis in the United States.

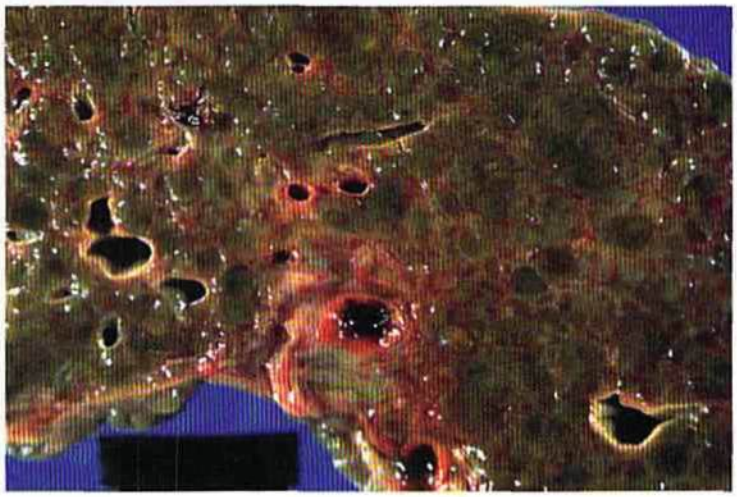


FIGURE 3-54. Close-up view demonstrating micronodular (less than 3 mm) and macronodular cirrhosis. Bile stasis is present (which stains the specimen green). (Image courtesy of PEIR Digital Library [http://peir.net].)

TABLE 3-16. Etiologies Causing Cirrhosis

Type of Cirrhosis	Causes
Infectious	**Viral hepatitis**, brucellosis, capillariasis, echinococcosis, schistosomiasis, toxoplasmosis.
Inherited/metabolic disorders	AAT, Alagille's syndrome, biliary atresia, Fanconi's syndrome, **hemochromatosis, Wilson's disease,** glycogen storage disease.
Drugs/toxins	**Alcohol**, amiodarone, arsenic, oral contraceptive pills, pyridinoline.
Other	**Heart failure** with long-standing congestion of the liver, **biliary obstruction,** CF, graft-versus-host disease, NASH, **primary sclerosing cholangitis,** sarcoidosis.

FLASH BACK

Portal to IVC anastomoses (collaterals):

- **Esophagus:** Left gastric vein to esophageal vein leads to **esophageal varices.**
- **Umbilicus:** Paraumbilical vein to superficial and inferior epigastric veins leads to **caput medusae.**
- **Rectum:** Superior rectal vein to middle and inferior rectal veins leads to **hemorrhoids.**

FLASH BACK

Portal hypertension in the context of CHF:

- Prolonged right-sided failure with retrograde transmission of venous pressure via the IVC.
- Liver sinusoids dilated/engorged with blood, leading to liver swelling and centrilobular fibrosis/alternating congestion **("nutmeg liver").**
- Hepatic failure, pulsatile liver.
- Firm, enlarged liver with signs of chronic liver disease in patients with CHF.

Presentation

Cirrhosis has a variety of manifestations:

- **Clinical presentation:** Complex, resulting from severely impaired liver function (hepatocellular damage), consequences of diffuse hepatic tissue scarring with portal hypertension, or a combination of both.

Impaired Liver Function (Hepatocellular Damage)

- **Jaundice** and **pruritus** resulting from the inability of the liver to conjugate bilirubin.
- **Hypoalbuminemia** as a result of impaired albumin synthesis.
- **Hyperestrogenism,** which causes **spider hemangiomas, palmar erythema, gynecomastia,** and **hypogonadism.**
- **Anemia** from folate deficiency.
- **Coagulopathies** from decreased production of clotting factors.

Consequences Of Diffuse Hepatic Tissue Scarring With Portal Hypertension (See Figure 3-55).

Clinical features of portal hypertension develop chiefly as a result of the establishment of portosystemic collaterals.

- **Gastroesophageal varices** with the potential for significant bleeding.
- Hemorrhoids.
- Periumbilical venous collaterals (**caput medusae**).
- **Splenomegaly** resulting in **thrombocytopenia.**

Additional sequelae include ascites, peripheral edema, and/or hydrothorax (see Figure 3-56):

- **Hypoalbuminemia** leads to decreased intravascular oncotic pressure and, along with **portal hypertension,** contributes to the formation of **ascites.** Ascitic fluid can become infected, causing **spontaneous bacterial peritonitis.**
- **Hepatic encephalopathy:** Severe loss of hepatic function leads to **shunting** of blood around the liver, leading to accumulation of toxic metabolites in the blood (**ammonemia**), causing brain toxicity.
- **Hepatorenal syndrome:** Increased portal venous pressure leads to decreased effective intravascular volume and decreased renal perfusion pressure (due to intrarenal redistribution of blood flow). Renal failure can thus develop in the presence of liver failure without intrinsic renal problems.

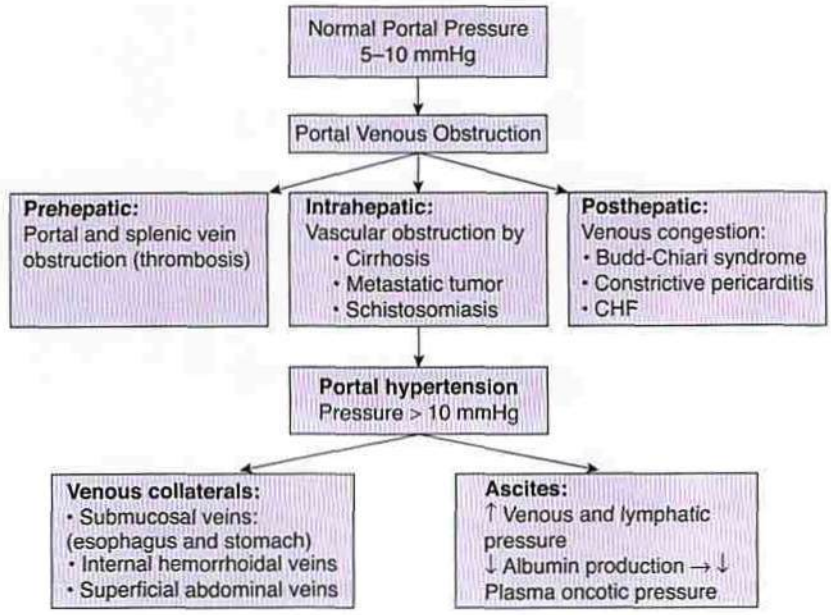


FIGURE 3-55. Pathophysiology of portal hypertension.

PATHOHISTOLOGY

Bridging fibrosis and small **regenerative nodules** (see Figure 3-57).

- Represent hepatocytic reaction to injury.
- Lack of normal liver cytoarchitecture (no portal triads and sinusoids).

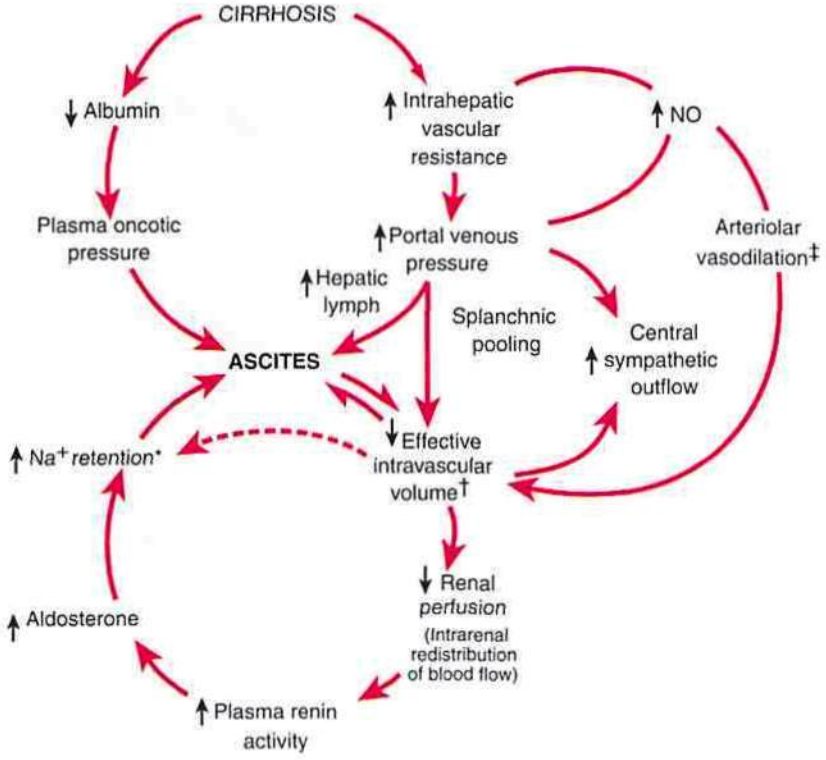


FIGURE 3-56. Multiple factors involved in the development of ascites. NO = Nitric oxide. (Modified, with permission, from Kasper DL, Braunwald E, Fauci AS, et al., eds, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 1865.)

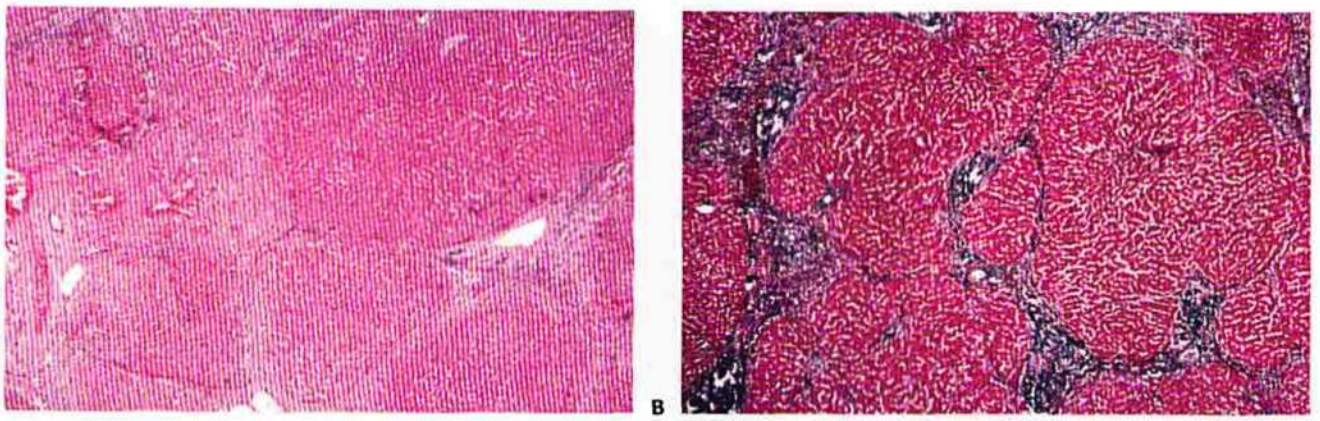


FIGURE 3-57. Histologic features of cirrhosis. (A) Prominent fibrous bands, some containing proliferating bile ductules, are interposed between islands of regenerating liver cells (H & E stain). (B) The fibrosis can be better appreciated on Masson's trichrome stain (blue color). (Image courtesy of PEIR Digital Library [http://peir.net].)

CLINICAL CORRELATION

Cirrhosis leads to a complete disarray of liver function, and thus elevated ALP, bilirubin, γ-glutamyl transferase, and PT, as well as anemia, thrombocytopenia, hypoalbuminemia, and hyponatremia.

KEY FACT

AST:ALT ratio of > 2.0 (cutoff > 1.5) is highly suggestive of alcoholic cirrhosis.

- Contribute to increased intrasinusoidal pressure (intrasinusoidal hypertension).

Diagnosis

- **Physical exam** may reveal any of the signs and symptoms mentioned above as evidence of liver disease.
- The **damaged liver** may be enlarged and tender.
- A **cirrhotic liver** will be shrunken, firm, and nodular.
- **Lab tests** may reveal elevated AST and ALT, but normal values do not rule out cirrhosis, as these values will return to normal as the hepatocytes "burn out."
- While not used for diagnosis, **RUQ ultrasound** will show the nodules characteristic of cirrhosis. Ultrasound can also be used to evaluate for splenomegaly, ascites, portal vein thrombosis, and HCC.
- The **gold standard** for diagnosing cirrhosis remains **tissue biopsy.** However, biopsy is not necessary if the patient's presentation and workup are both consistent with cirrhosis.

Treatment

- For complications of cirrhosis: Sclerotherapy or banding for symptomatic esophageal varices, drainage of excess peritoneal fluid for ascites (called **paracentesis**), nutritional support.
- Treatment of hepatic encephalopathy: lactulose (reduces the ammonia production of colonic bacteria), neomycin (decrease the colonic concentration of ammoniagenic bacteria).
- Procedures that allow blood to bypass the portal venous system, thus relieving the symptoms and complications of portal hypertension, are also used, such as portacaval shunting (more invasive) and transjugular intrahepatic portosystemic shunting (less invasive).

Prognosis

Can be fatal if it progresses to liver failure or HCC. Cirrhosis is not uniformly fatal.

Primary Biliary Cirrhosis (PBC)

PBC is characterized by destruction of the small- and medium-sized bile ducts in the liver, resulting in **intrahepatic cholestasis.** PBC has a poorly understood pathophysiology; however, it is frequently associated with a variety of autoimmune disorders, thus suggesting an autoimmune etiology. It primarily affects middle-aged women (35–60 years of age).

Presentation

Most cases are asymptomatic for a prolonged period. **Symptoms develop gradually** as the disease progresses and reflect progressive liver damage. Symptoms range from severe pruritus, jaundice, malabsorption, and fatigue to signs of hepatocellular failure and portal hypertension.

Diagnosis

The **most classic lab** abnormality is an **extreme elevation in ALP**, along with elevated AST and ALT, cholesterol (especially HDL), **IgM**, and cryoglobulins. **Antimitochondrial antibodies** are highly specific for this disease.
Liver biopsy will confirm the diagnosis: Lymphocytic infiltrates in the portal regions and loss of bile ductules in the liver parenchyma.

Treatment

There are no therapies that can halt or reverse PBC; it is possible only to provide symptomatic relief and slow the progression of disease. Liver transplantation is the only life-saving treatment currently available.

Prognosis

Progressive disease that ultimately leads to cirrhosis of the liver.

INBORN ERRORS OF METABOLISM

Hemochromatosis

An inherited, **autosomal recessive,** male-predominant metabolic disorder of iron storage, characterized by increased intestinal iron absorption. Hemochromatosis is equally prevalent in all races and both genders. Mutations affect the *HFE* gene, which causes decreased affinity for the transferrin receptor to bind transferrin.
Excessive serum levels of iron lead to deposition in and damage to several major organs, including the liver, pancreas, heart, joints, and pituitary gland.

Presentation

Organ damage does not become apparent until patients are at least 40 years of age. Early signs include weakness, weight loss, abdominal pain, and loss of libido.

- **Cirrhosis** with iron deposits (see Figure 3-58) affecting the hepatocytes and resulting in hepatomegaly and stigmata of chronic liver disease.
- Iron deposition in **pancreatic islet cells** can lead to type 1 diabetes mellitus (DM-1).
- **Iron deposition** in the skin and **increased melanin production** cause darkening of the skin—bronze skin discoloration (hence, the name **bronze diabetes**).
- Significant risk of **heart failure.**

CLINICAL CORRELATION

Suspect **PBC** in women with a history of **Sjögren's syndrome, Raynaud's syndrome, or scleroderma.**

FLASH BACK

Histologic findings in **PBC resemble** those of **graft-versus-host (GVH) disease.**

KEY FACT

Check for γ-glutamyl transpeptidase (specific to the hepatobiliary system) to differentiate hepatobiliary involvement from other pathologies.

KEY FACT

Circulating IgG anti-mitochondrial antibody is detected in > 90% of cases.

KEY FACT

- Clinical symptoms of hemochromatosis: Males >> females; menses causes loss of iron.
- Females are clinically affected after menopause.

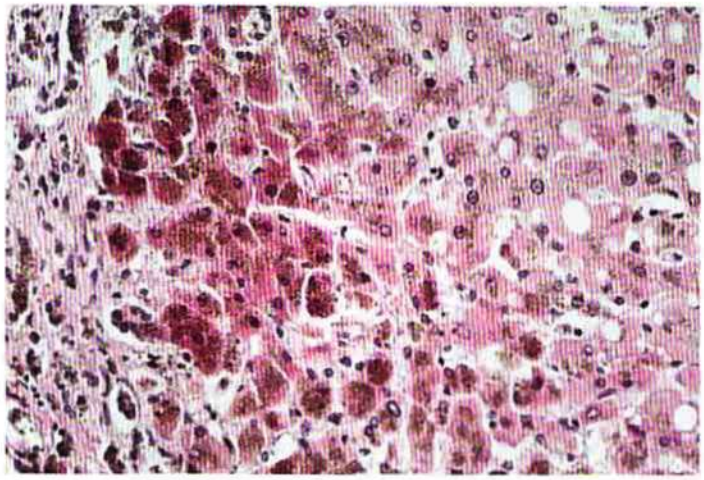


FIGURE 3-58. Hemosiderin-laden hepatocytes indicative of hemochromatosis. (Image courtesy of PEIR Digital Library [http://peir.net].)

CLINICAL CORRELATION

Distinguish between:
Hemochromatosis = Inherited disorder
Hemosiderosis = Acquired disorder of iron overload (e.g., due to repeated blood transfusions in patients with thalassemia).

Diagnosis

- Clinical presentation.
- Elevated percentage of transferrin saturation (> 50%).
- Elevated serum iron and ferritin.
- Iron:total iron-binding capacity ratio > 50%.
- Urinary iron.
- Confirm with liver biopsy (see Figure 3-64).

Treatment

- Intermittent phlebotomy to remove excess body iron
- Chelating agents (deferoxamine)
- Abstinence from alcohol consumption (increases iron absorption)
- Supportive treatment of common complications (i.e., diabetes, CHF)

CLINICAL CORRELATION

High levels of copper in serum are a result of inadequate copper excretion in the liver.

Wilson's Disease (Hepatolenticular Degeneration)

An inherited (**autosomal recessive**) metabolic disorder characterized by excessive serum levels of **copper** with deposition in major organs (primarily liver, brain, kidneys, and corneas). Chronic disease that is fatal without treatment.

Wilson's disease develops as a result of a mutation in the ***ATP7B* gene** on **chromosome 13 (13q14.3)**, which codes for a **P-type ATPase** that transports copper into bile and incorporates it into ceruloplasmin. The mutant form of *ATP7B* inhibits the release of copper into bile.

CLINICAL CORRELATION

Copper fails to enter the circulation as ceruloplasmin, which leads to **low levels of ceruloplasmin in serum.**

Presentation

Suspect Wilson's disease in **young adult patients** who present with stigmata of liver disease along with neurologic changes.

- Classically, patients have **Kayser-Fleischer rings** (deposits of copper on the outer edges of the corneas) on ophthalmologic exam (**slit-lamp** examination).
- Liver disease can present in the form of hepatitis, cirrhosis, or decompensation.
- Neurologic changes resulting from copper accumulation in the brain.

Diagnosis

- Decreased serum ceruloplasmin levels.
- Increased serum and urine copper levels.
- Confirm with liver biopsy.

Treatment

- Avoid copper-rich foods.
- Copper **chelators,** primarily **penicillamine.** Alternative agents include potassium sulfide, pyridoxine, and zinc acetate.

HEPATIC TUMORS

Can be either primary tumors (derived from liver cells) or metastatic tumors. **The most common tumors of the liver are metastatic (i.e., colon cancer).**

Benign Liver Tumors

The most common benign tumors include hepatocellular adenoma (HA) and focal nodular hyperplasia (FNH).

Hepatocellular Adenoma

Seen predominantly in women in the third and fourth decades; **oral contraceptives** are implied as an etiologic factor. Risk is increased in anabolic steroid users and in those with glycogen storage disease type I.

KEY FACT

Hepatocellular Adenoma: Linked to hormonal influence; oral contraceptives are thought to play an etiologic role.

Focal Nodular Hyperplasia

As with HA, **FNH** also occurs primarily in women, but is **not associated** with the use of oral contraceptives.

Presentation

- **HA:** Primarily in the right liver lobe and often large (> 10 cm). Clinical features include pain and palpable mass or signs of intratumor hemorrhage.
- **FNH:** Generally asymptomatic and incidental finding on imaging studies as a solid tumor in the right lobe consisting of a fibrous core with stellate projections.

Histology

Both tumors consist of normal or slightly atypical hepatocytes; however, **FNH** also **contains biliary epithelium** and **Kupffer cells.** Hepatocytes contain increased glycogen, appearing paler and larger than normal.

KEY FACT

Kupffer cells are characteristically absent in HA.

Diagnosis

CT, MRI, and selective hepatic angiography are used to make the diagnosis.

- Hypervascular appearance on angiography.
- Technetium scans typically show **uptake in FNH** due to the presence of Kupffer cells, but lack of uptake in HA.

Treatment

Regular imaging to follow progression of small tumors. If the lesion is > 8–10 cm, near the surface, and resectable, then surgical removal is appropriate.

- Patients should stop taking oral contraceptives.

KEY FACT

Risk factors for HCC:
Anything that causes chronic liver disease can lead to HCC:

- Hepatitis B
- Hepatitis C
- Aflatoxin B1, which is found in peanuts affected by mold (*Aspergillus* in China and Africa)
- Hemochromatosis
- Tyrosinemia
- Cirrhosis
- α_1-Antitrypsin deficiency
- Long-term androgenic steroid use

CLINICAL CORRELATION

Maintain a high index of suspicion with **cirrhotic patients** who exhibit **clinical changes,** such as new-onset encephalopathy, ascites, jaundice, or variceal bleeding.

KEY FACT

High levels of AFP (> 500–1000 µg/L) in an adult with liver disease and no obvious GI tumor strongly suggest HCC.

- Pregnancy increases the risk of hemorrhage; women with large adenomas should be counseled to avoid pregnancy.

Prognosis

The risk of malignant change is small, although it is increased with multiple tumors and tumors > 10 cm.

Malignant Liver Tumors

The two most common types of liver carcinoma are primary HCC and metastatic carcinoma. Other malignant neoplasms include cholangiocarcinoma, carcinoma of the papilla of Vater, and cancer of the gallbladder.

Hepatocellular Carcinoma (Hepatoma)

HCC is one of the most common tumors in the world, with the highest prevalence in Asia and sub-Saharan Africa due to the high prevalence of **hepatitis B and C**; it is less common in the United States and western Europe. It is four times more common in men.

Presentation

Symptoms are similar to those of chronic liver disease. The most common presenting symptoms are pain or mass in the right upper quadrant. **Physical exam** may reveal friction rub or bruit over the liver. **Elevations** of **AFP** and **ALP** are common.

Diagnosis

Based on imaging (see Figure 3-59), and elevated serum AFP levels. Any solitary nodule seen on CT of a cirrhotic patient should be worked up for HCC.

- **Liver biopsy** is the gold standard. **Histologically,** the tumor ranges from well differentiated (see Figure 3-60) to poorly differentiated, and often has central areas of necrosis in large tumors. Bile globules and acidophilic inclusions are sometimes present.

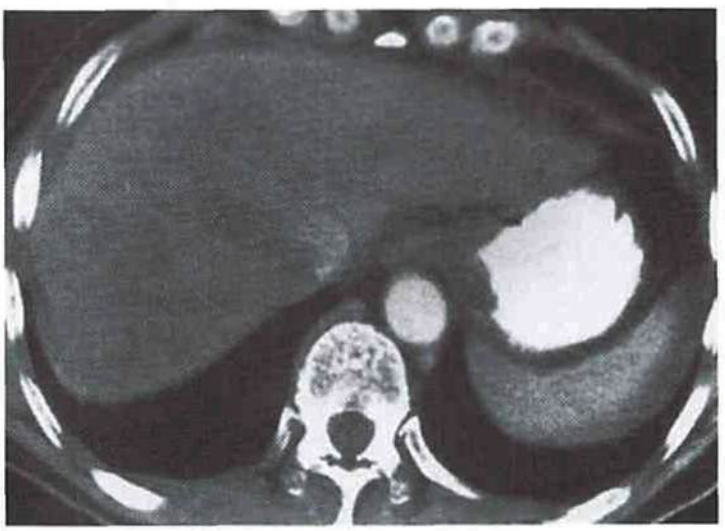


FIGURE 3-59. Focal lesion within the right lobe of the liver, which is associated with a clot entering the hepatic vein and even the inferior vena cava, findings typical of hepatocellular carcinoma. (Reproduced, with permission, from Chen MYM, Pope TL Jr, Ott DJ. *Basic Radiology*, New York: McGraw-Hill, 2004: 293.)

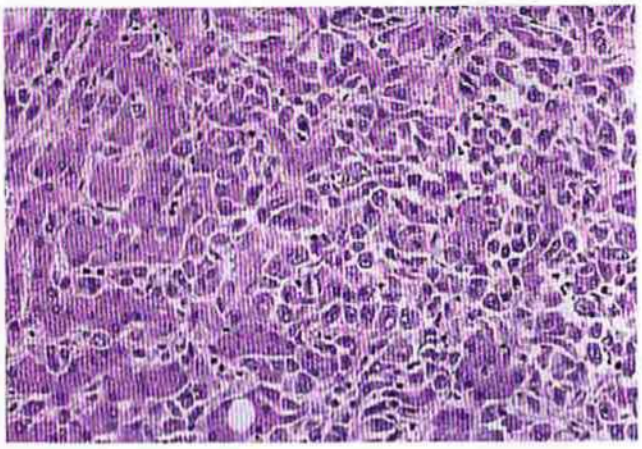


FIGURE 3-60. Photomicrograph with standard H & E stain of hepatocellular carcinoma cells in hepatic parenchyma. (Reproduced, with permission, from Kantarjian HM, Wolff RA, Koller CA. MD *Anderson Manual of Medical Oncology*. New York: McGraw-Hill: 2006.)

Treatment

Depending on TNM classification, treatment options include partial hepatectomy, liver transplantation, radiofrequency ablation, or percutaneous acetic acid or ethanol ablation.

Prognosis

Usually diagnosed late, when distant metastases (lung, brain, bone, and adrenal) have occurred. The median life expectancy after diagnosis is 6–20 months.

Metastatic Tumors

In the United States, the incidence of metastatic carcinoma is at least **20 times greater** than that of primary HCC. The most common metastases (see Figure 3-70) include tumors from the **GI, lung, and breast,** and **melanoma.**

Presentation

Mostly symptoms reflecting the primary tumor, but may present with nonspecific symptoms of weakness, weight loss, fever, sweating, and loss of appetite. Liver biochemical tests are often abnormal, but mildly elevated and nonspecific.

Diagnosis

Evidence of metastatic disease to the liver should be sought for any patient with primary malignancy, especially of the lung, GI tract, or breast.

Treatment

Most metastatic carcinomas respond poorly to all forms of treatment, which is usually only palliative, with the exception of metastatic colon cancer, with a 5-year survival rate of at least 25% after resection.

Other Liver Tumors

Hemangioma: Benign and generally left untreated.
Cholangiocarcinoma: Liver flukes (*Clonorchis sinensis*) increase risk in immigrants.

FLASH BACK

Liver is the most common site of metastasis for GI (and other) tumors due to its size, high rate of blood flow, unique dual blood supply, and cytoarchitecture.

MNEMONIC

Metastases >> Primary liver tumors
Cancer **S**ometimes **P**enetrates **B**enign **L**iver (**C**olon > **S**tomach > **P**ancreas > **B**reast > **L**ung)

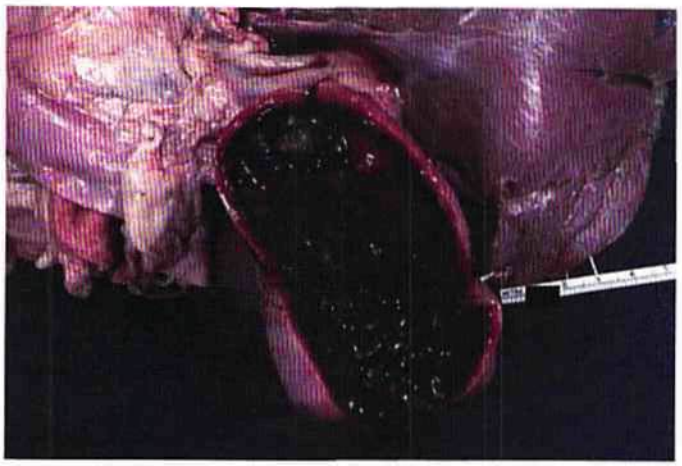


FIGURE 3-61. Chronic cholecystitis and cholelithiasis. Gallbladder with obviously thickened wall and filled with faceted black calculi. (Image courtesy of PEIR Digital Library [http://peir.net].)

Angiosarcoma: Vinyl chloride use.
Hepatoblastoma: Main primary liver tumor in **children.**

CHOLELITHIASIS

Gallstones are a common cause of RUQ pain and are classically found in patients who are overweight, middle-aged, and female. About 10%–20% of Americans have gallstones, and about 50% of those people eventually have symptoms.

There are three types, including cholesterol stones, mixed stones, and pigment (bilirubin) stones (see Figure 3-61 and Table 3-17).

Stones form when there is a disruption in cholesterol transport from the liver into the bile; this process is coupled with a simultaneous secretion of phospholipid and bile salts. Disruption of the **cholesterol:bile salt ratio** leads to cholesterol precipitation in the gallbladder, thus enabling the formation of stones.

TABLE 3-17. Types of Gallstones and Typical Findings

	Components	Risk Factors	Radiography
Cholesterol stones	Cholesterol	CD, CF, clofibrate (decreases plasma cholesterol), estrogen, multiparity, rapid weight loss, Native American heritage, advanced age.	Mostly **radiolucent** (cannot be seen); **10%–20%** are **opaque** due to calcifications.
Mixed stones, most common types	Cholesterol and pigment	Most common.	**Radiolucent.**
Pigment	Pigment (bilirubin)	Chronic RBC hemolysis, alcoholic cirrhosis, advanced age, biliary infection.	**Radiopaque** (seen on radiograph).

- **Cholesterol load > bile salts:** Bile salts and lecithin are unable to solubilize the cholesterol.
- **Disrupted bile salt production** (decreased bile acid absorption from the intestine or hepatic failure) leads to increased cholesterol:bile salt ratio.

MNEMONIC

Risk factors for gallstones (4 Fs):

Fat
Fertile
Female
Forties

PRESENTATION

Be suspicious of gallstones in patients with RUQ pain. The pain is usually worse after meals (**postprandial pain**) and can be associated with nausea/vomiting and fatty food intolerance.

DIAGNOSIS

Ultrasound is the best way to visualize gallstones. **Radiography** can be deceiving because most gallstones are radiolucent and may not appear on abdominal X-ray. Endoscopic retrograde cholangiopancreatography (**ERCP**) is a procedure that can visualize the presence of gallstones in the common bile duct (see Figure 3-62).

TREATMENT

Elective cholecystectomy (removal of the gallbladder) in symptomatic patients. Some patients may not require surgery but should modify their diet and avoid fatty food.

PROGNOSIS

The prognosis is good, but there are many potential complications:

- Recurrent biliary colic (intermittent pain).
- Acute cholecystitis (prolonged blockage of the cystic duct, causing gallbladder inflammation or infection).
- Choledocholithiasis (gallstone obstructing the common bile duct).
- Acute cholangitis (bacterial infection of the biliary tree).
- Gallstone ileus and gallstone pancreatitis.

CHOLECYSTITIS

Inflammation of the gallbladder is a common complication of cholelithiasis.

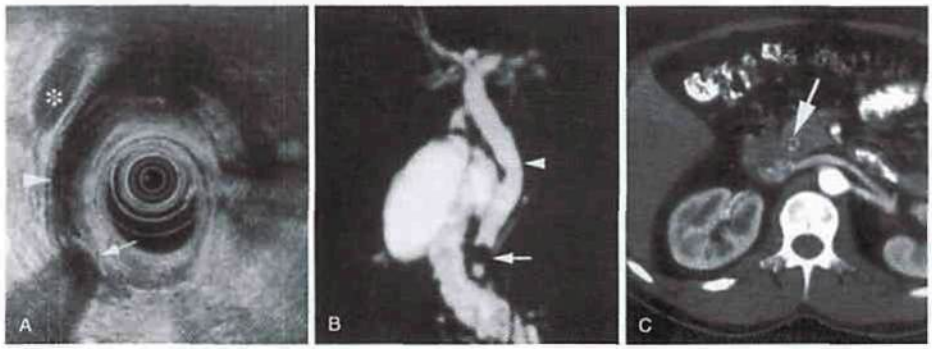


FIGURE 3-62. Methods of bile duct imaging. Arrows mark bile duct stones. Arrowheads indicate the common bile duct, and the asterisk marks the portal vein. (A) Endoscopic ultrasonography (EUS). (B) Magnetic resonance cholangiography (MRCP). (C) Helical computed tomography. (Reproduced, with permission, from Kasper DL, Braunwald E, Fauci AS, et al., eds, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 1736.)

CLINICAL CORRELATION

- **Charcot's triad** (cholangitis):
  Right upper quadrant pain
  Fever
  Jaundice
- **Reynolds' pentad** = Charcot's triad + Shock and altered mental status

KEY FACT

"Sonographic" Murphy's sign when it occurs during ultrasound examination.

KEY FACT

Positive HIDA scan = Obstruction in passage = Nonvisualization of gallbladder confirms diagnosis.

MNEMONIC

Causes of acute pancreatitis: **GET SMASHED.**

Gallstones
Ethanol
Trauma
Steroids
Mumps
Autoimmune disease
Scorpion sting
Hypercalcemia/**H**yperlipidemia
ERCP
Drugs

KEY FACT

Dideoxyinosine can cause fatal pancreatitis!

Presentation

Very similar to that of cholelithiasis: Postprandial colicky RUQ pain radiating to the right scapula, as a result of intermittent blockage of the common bile duct. Nausea/vomiting and bloating can also be present.

- Jaundice may occur as a result of complete blockage of the common bile duct, leading to infection or **cholangitis.**
- **Charcot's triad**: epigastric/RUQ pain, fever, and jaundice may indicate the presence of cholangitis.

Diagnosis

Classic physical exam feature is **Murphy's sign.**

- **Elicitation:** Palpate the right subcostal area (gallbladder fossa) while the patient inspires deeply; the gallbladder descends toward the examiner's fingers.
- **Positive response:** The patient feels increased discomfort and/or pain upon this maneuver and may have an associated inspiratory arrest.

Ultrasound exam can show stones in the gallbladder, thickening of the gallbladder wall, and edema. HIDA scan (**cholescintigraphy**) is more sensitive for cholecystitis and can clinch the diagnosis.

Treatment

Start antibiotics (usually against gram-negative bacteria, such as *E. coli* and *Klebsiella*, empirically), and perform cholecystectomy once the patient is stable.

EXOCRINE PANCREAS

Acute Pancreatitis

Caused by activation of pancreatic enzymes, which leads to **pancreatic autodigestion** with **hemorrhagic fat necrosis.**

Presentation

Classically presents as sudden-onset, boring epigastric abdominal pain radiating to the back and flanks accompanied by anorexia and nausea. May occur following a large meal or drinking binge.

Diagnosis

Clinical symptoms and imaging:

- Leukocytosis and elevated serum amylase (> 3 times upper limit of normal) and lipase (with higher specificity and persisting longer) should be expected.
- **Histology:** Fat necrosis with pale basophilic calcium soaps, hemorrhage, necrotic debris, and inflammatory response (see Figure 3-63).
- Abdominal X-ray may show localized ileus (**sentinel loop**) in C-loop of duodenum.
- Contrast-enhanced CT is recommended for severe pancreatitis in order to rule out pseudocyst and fully visualize the extent of disease.

Treatment

Rest, gastric suction, fluid and electrolyte replacement, and pain control with opioids (**meperidine**).

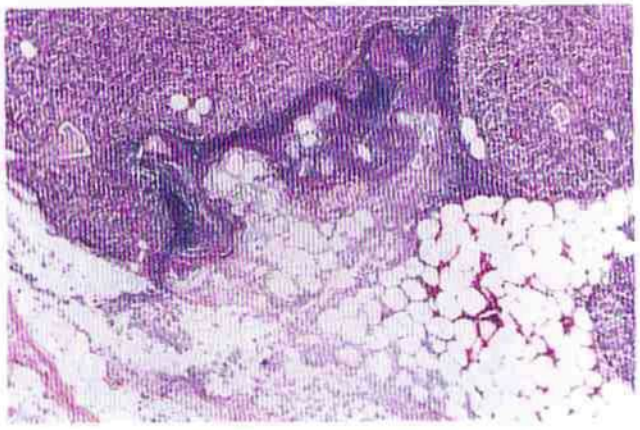


FIGURE 3-63. Acute pancreatitis with extensive fat necrosis. Normal peripancreatic fat, fat necrosis with pale basophilic calcium soaps, hemorrhage, necrotic debris, inflammatory response, and normal pancreas. (Image courtesy of PEIR Digital Library [http://peir.net].)

- Surgical treatment is only for trauma, ductal stones, obstructive lesions, and infected pancreatic necrosis.

Prognosis

About 20%–30% of patients may have complications of necrosis, organ failure, or both, including DIC, acute respiratory distress syndrome (ARDS), diffuse fat necrosis, hypocalcemia, pseudocyst formation, hemorrhage, and infection.

- About 10% of patients with pancreatic cancer present with acute pancreatitis. Suspect it in older patients with no other risk factors.

Chronic Pancreatitis

Chronic pancreatitis may present as episodes of acute inflammation in a previously injured pancreas or as chronic damage with persistent pain or malabsorption. The causes are similar to those of acute pancreatitis.

- In the United States, **alcoholism** is the most common cause in **adults.**
- CF is the most common cause **in children.**

Presentation

Epigastric pain **radiating to the back**; often not present in chronic disease.

- More common type of pain is persistent, deep-seated, and unreponsive to antacids; worsened by ingestion of fatty foods or alcohol.
- Symptoms of **pancreatic insufficiency** include **steatorrhea,** weight loss, and deficiencies of fat-soluble vitamins (A, D, E, and K).

Diagnosis

In **contrast to acute pancreatitis,** serum amylase and lipase are usually not elevated. The classic triad includes progressive parenchymal fibrosis with **pancreatic calcification, steatorrhea, and DM.**

- Radiographic hallmark is the presence of scattered calcifications (see Figure 3-64).

Treatment

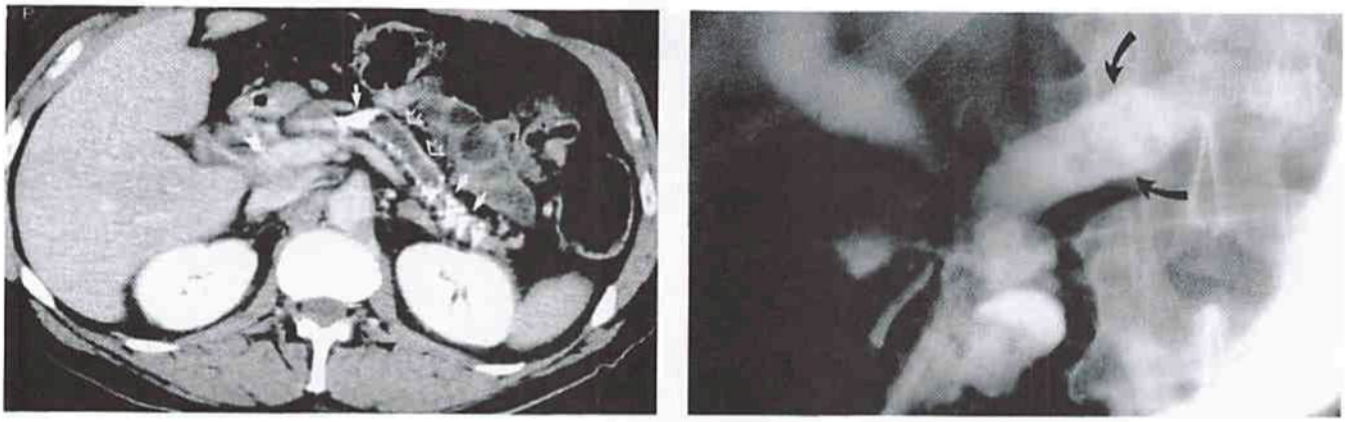
Address the two major problems: **pain and malabsorption.**

FLASH BACK

- **Morphine** may cause **spasm** of the sphincter of Oddi and worsen pain.
- **Meperidine** is the preferred analgesic for treating the pain of acute pancreatitis because it **does not cause spasm of the sphincter of Oddi.**

KEY FACT

The primary defect may be inspissated enzymes in the ducts, leading to ductal obstruction and ductal dilation, diffuse atrophy of acinar cells, fibrosis, and eventual calcification that leads to chronic pain and pancreatic insufficiency.



A B

FIGURE 3-64. Chronic pancreatitis and pancreatic calculi. CT scan and ERCP appearance. (A) There is evidence of an atrophic pancreas with multiple calcifications (arrows). Note the markedly dilated pancreatic duct seen in this section through the body and tail (open arrows). (B) ERCP in the same patient demonstrates the dilated pancreatic duct as well as an intrapancreatic duct calculus (arrows). (Reproduced, with permission, from Fauci AS, Kasper DL, Braunwald E, et al, eds. *Harrison's Principles of Internal Medicine*, 17th ed, New York: McGraw-Hill, 2008: Figure 307-4.)

- **Pain:** Avoid alcohol and large meals. Use of narcotics can often lead to opiate addiction and has led to the use of palliative procedures (resection of strictures, stent placement, and ductal decompression).
- **Malabsorption:** Enzyme replacement and dietary fat restriction.

Prognosis

Patients who abstain from alcohol and use vigorous replacement therapy do reasonably well.

Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma is a malignancy of the exocrine portion of the pancreas; it is one of the most deadly cancers (5-year survival rate of < 5%).

- **Risk factors:** Age, smoking, family history, and chronic pancreatitis associated with alcohol abuse.

Several mutations have been associated with pancreatic adenocarcinoma, the most common of which is the *K-RAS* gene mutation.

Presentation

Tumors are located in the head of the pancreas 75% of the time, giving the classic presentation of **painless obstructive jaundice**, and are silent until late in the disease progression. Common signs and symptoms include unexplained weight loss, malaise, epigastric pain that radiates to the mid-back, and signs of obstructive jaundice. Other signs include **migratory phlebitis** (**Trousseau's sign**) and, occasionally, the onset of DM.

Diagnosis

No lab test is specific for pancreatic cancer, although elevated bilirubin and ALP confirm biliary obstruction.

- The best tumor marker for pancreatic cancer is **CA 19-9**; it is not diagnostic, but can be used to monitor progression of the disease.
- CT scan is the most common imaging study used for diagnosing pancreatic cancer (see Figure 3-65). Other studies include ERCP (during which a biopsy can be taken), MRI, and endoscopic ultrasound.

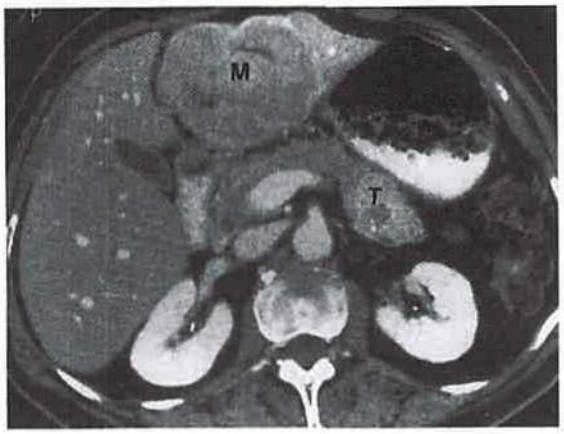


FIGURE 3-65. Focal lesion occupying the left lobe of the liver (M) and a focal enhancing mass in the pancreatic tail (T), representing a pancreatic neoplasm metastatic to the liver. (Reproduced, with permission, from Chen MYM, Pope TL, Ott DJ, *Basic Radiology*, New York: McGraw-Hill, 2004: 293.)

Treatment

Surgical resection, called a pancreaticoduodenectomy (Whipple's operation), is the only treatment that has had any success in prolonging survival. Chemotherapy and radiation have had minimal success.

Prognosis

Pancreatic cancer has a dismal prognosis, with death usually occurring within 1 year of diagnosis.

ENZYME MARKERS OF GI PATHOLOGY

Enzyme Markers

Commonly used laboratory assays (see Table 3-18) available in most clinical practices include serum **AST, ALT, γ-glutamyl transferase**, bilirubin, **ALP, amylase, lipase, and PT.** Other, more specialized markers (i.e., **ceruloplasmin** with Wilson's disease) are used when rare conditions are suspected.

Many of these enzyme markers can be affected by pathologies outside the gut. Therefore, the differential diagnosis must include both extrinsic (outside the GI tract) and intrinsic (within the GI tract) pathologies.

Aspartate Aminotransferase (AST)

Anatomic Significance

Intracellular **(cytosol and mitochondria)** enzyme found in liver cells, but also in skeletal muscle, heart, brain, and RBCs.

Physiologic Action

Catalyzes the transfer of amino groups to form pyruvate.

Lab Test Interpretation

Increased concentration in the bloodstream with **tissue** (especially liver) **damage.** Tissue damage may occur with liver damage, or with cor pulmonale *(right heart failure), myocardial ischemia, and extensive trauma.*

TABLE 3-18. Key Enzyme Markers of GI Pathologies

Enzyme Marker	Range of Normal Values	Key Pathologies Indicated by Abnormality
AST	0–35 IU/L	Increased in liver damage (any etiology).
ALT	0–35 IU/L	Increased in liver damage (any etiology).
GGT	9–85 IU/L	Increase specific for liver disease (any etiology).
Bilirubin ▪ Direct ▪ Indirect ▪ Total	0.1–0.4 mg/dL 0.2–0.7 mg/dL 0.1–1.2 mg/dL	
AP	41–133 IU/L	Nonspecific indicator of tissue damage (liver, bone, or intestinal); also increased in pregnancy.
Amylase	20–110 IU/L	Increased in pancreatic pathologies, intestinal disease, and ruptured ectopic pregnancy.
Lipase	0–160 IU/L	Increased in pancreatitis (acute and chronic); also increased in other pancreatic pathologies.
PT	11–15 s	Increased in liver disease and warfarin therapy.
Ceruloplasmin	20–35 mg/dL	Decreased in Wilson's disease (hepatolenticular degeneration).

Alanine Aminotransferase (ALT)

Anatomic Significance

Intracellular (**cytosol**) enzyme; relatively specific to the liver. Also found in kidney cells, skeletal muscle, and cardiac tissue.

Physiologic Action

Catalyzes the transfer of amino groups to form oxaloacetate.

Lab Test Interpretation

Increased along with AST in the bloodstream with **tissue** (especially liver) **damage.** Levels approximate the magnitude of liver damage. Also increased with right heart failure, myocardial ischemia, and extensive trauma.

AST:ALT Ratio

Individually, abnormal values of AST or ALT are relatively nonspecific measures of liver damage. Certain characteristics in the pattern of elevation and the ratio of AST to ALT, however, enable clinical correlations to be made (see Table 3-19).

TABLE 3-19. AST:ALT Ratio

Mild AST:ALT Elevation (< 5× Upper Normal Limit)	Severe AST:ALT Elevation (> 15× Upper Normal Limit)	Extreme AST and ALT Elevation (AST and ALT ≥ 1000)	Nonhepatic Causes of AST:ALT Abnormalities
Wilson's disease Chronic hepatitis (viral, alcoholic, etc.)	Wilson's disease Acute viral hepatitis	Acute viral hepatitis Acute toxic injury (i.e., acetaminophen poisoning)	Drugs (i.e., statins) Pregnancy
Ethanol α_1-Antitrypsin deficiency Toxins/drugs	Ischemic injury Toxins/drugs Budd-Chiari syndrome Autoimmune hepatitis Hepatic artery ligation	Acute ischemic injury	Myocardial infarct Muscle disorders

γ-Glutamyl Transferase

Anatomic Significance

Present in hepatic and biliary epithelial cells.

Physiologic Action

Induced by alcoholic intake.

Lab Test Interpretation

Increased in liver disease. γ-Glutamyl transferase is sensitive, but is **not specific**, for liver disease. Best tool to assess recent alcohol use.

Alkaline Phosphatase

Anatomic Significance

Synthesized in liver, bone, intestine, and placenta.

Physiologic Action

Nonspecific indicator of tissue damage (liver, bone, intestine, and/or placenta).

Lab Test Interpretation

Increased in **obstructive hepatobiliary disease.** Also increased in bone disease (i.e., Paget's disease, bone metastases), hyperparathyroidism, **pregnancy (third trimester)**, and GI disease (i.e., perforated ulcer).

Amylase

Anatomic Significance

Synthesized primarily in the pancreas and salivary glands; however, also produced by the ovaries, intestines, and skeletal muscle.

Physiologic Action

Hydrolyzes complex carbohydrates.

Lab Test Interpretation

Increased in **pancreatic disease** (pancreatitis, pseudocyst, pancreatic duct obstruction, malignancy), **bowel obstruction or infarction, mumps, parotitis, peritonitis, and ruptured ectopic pregnancy. Decreased** in **pancreatic insufficiency and CF.**

Lipase

Anatomic Significance

Synthesized in the pancreas, liver, intestine, stomach, tongue, and other cells throughout the body.

Physiologic Action

Hydrolysis of glycerol esters and long-chain fatty acids.

CLINICAL CORRELATION

Lipase is considered the most specific test to detect pancreatitis.

Lab Test Interpretation

Increased in **pancreatic pathologies** (including acute/chronic pancreatitis, pseudocyst, and malignancy), **CF, intestinal malignancy, IBD, peritonitis, biliary disease, and liver disease.**

Prothrombin Time

Anatomic Significance

Synthesized in the liver.

Physiologic Action

Screening test used to evaluate the extrinsic pathway of the coagulation system and monitor warfarin therapy. Also a relatively rapid and sensitive indicator of hepatic capacity for protein synthesis, since the half-lives of factors II and VII are relatively short (hours).

Lab Test Interpretation

Increased with **liver disease, warfarin therapy, vitamin K deficiency, and intravascular coagulation.**

Ceruloplasmin

Anatomic Significance

Synthesized in the liver.

Physiologic Action

Main copper-carrying protein in serum.

Lab Test Interpretation

Decreased in **Wilson's disease**, malnutrition, nephrotic syndrome, and Menkes' disease (X-linked disorder of copper deficiency).

Pharmacology

This section describes the drugs used to treat the most common GI pathologies. Figure 3-66 summarizes the physiology of gastric secretions and the mechanism of action of respective compounds used in the treatment of certain GI diseases.

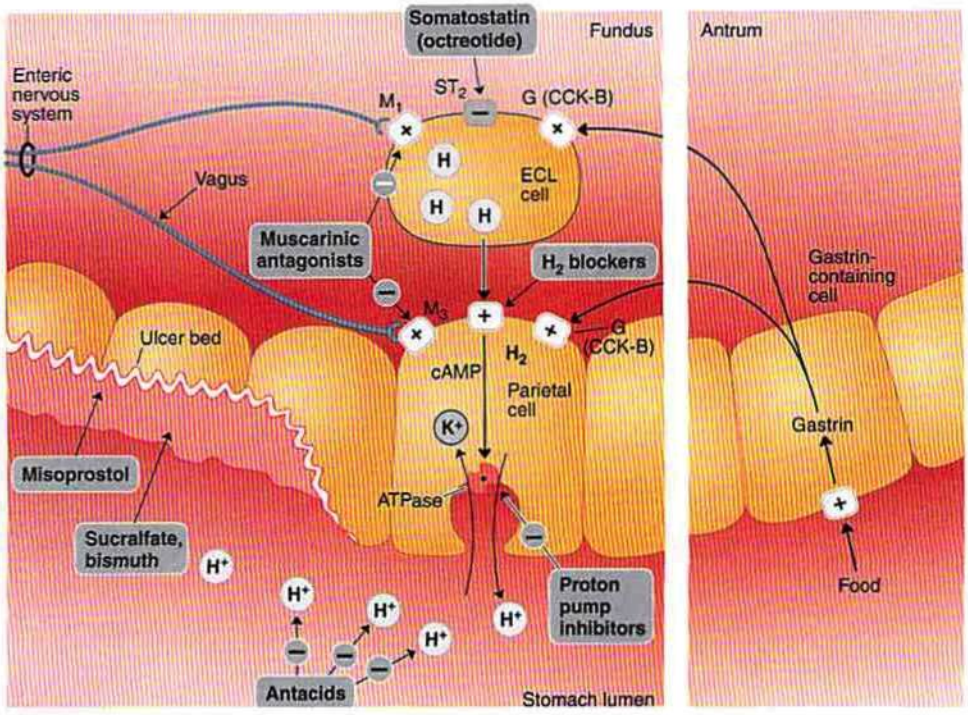


FIGURE 3-66. Summary of GI therapies. (Modified, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*. New York: McGraw-Hill, 2003: 159.)

HISTAMINE BLOCKERS

Key Drugs

Cimetidine, ranitidine, famotidine, nizatidine.

Mechanism

Reversible block of histamine H_2 receptors that leads to decreased H^+ secretion by the stomach parietal cells.

Uses

Treatment and maintenance therapy of PUD, GERD, and dyspepsia.

Side Effects

Cimetidine is a potent inhibitor of the cytochrome P-450 system. It is also a potent antiandrogenic and can lead to decreased renal creatinine clearance. The other H_2 blockers are relatively free of these side effects.

KEY FACT

Cimetidine can increase blood levels of other drugs cleared by the P-450 system (e.g., SSRIs, TCAs, phenytoin, and calcium channel blockers). Caution should be taken when using these drugs simultaneously.

PROTON PUMP INHIBITORS (PPIs)

Key Drugs

Omeprazole, lansoprazole, rabeprazole, esoprazole.

Mechanism

Irreversibly inhibits H^+-K^+-ATPase in the stomach parietal cells.

Uses

PUD, gastritis, esophageal reflux disease, and Zollinger-Ellison's syndrome.

KEY FACT

PPIs must be "turned on" by an acidic environment in the parietal cell compartment. Therefore, PPIs work poorly in patients with concomitant use of antisecretory agents (H_2 blockers).

Side Effects

Generally mild and include headache, nausea, and diarrhea.

BISMUTH AND SUCRALFATE

Mechanism

Bind to the ulcer base, providing a protective layer for the stomach, as well as allowing HCO_3^- secretion to restore the pH gradient in the mucus layer. Sucralfate suppresses *H. pylori* and inhibits acid secretion in infected patients with duodenal ulcers. Bismuth lacks antiacidic properties.

Uses

KEY FACT

Triple therapy for *H. pylori* ulcers: bismuth, metronidazole, and amoxicillin.

Binding agents commonly used to aid in ulcer healing as well as to treat traveler's diarrhea.

Side Effects

Sucralfate has minimal adverse side effects other than possible aluminum toxicity. Bismuth toxicity can occur in patients with renal failure.

MISOPROSTOL

Mechanism

Prostaglandin E_1 analog. Increases the production and secretion of the gastric mucus barrier and decreases acid production.

Uses

The main GI indication is the prevention of NSAID-induced peptic ulcers. Commonly used in the maintenance of a patent ductus arteriosus (PDA) and in the induction of labor.

Side Effects

Diarrhea and crampy abdominal pain. Contraindicated in women of childbearing age due to its abortifacient properties.

INFLIXIMAB

Mechanism

IgG-1 monoclonal antibody with a high specificity and affinity for TNF-α. Infliximab most likely works by destroying activated TNF-α cells through apoptosis or complement-mediated actions. TNF-α is found in the stool of patients with CD and may be correlated with disease severity.

Uses

Indicated for severe or fistulizing CD that is refractory to corticosteroids and sulfasalazine.

Side Effects

Infusion reactions, such as shortness of breath, hypotension, fever/chill, and urticaria, can occur. Delayed hypersensitivity reactions are marked by myalgia, fever, and rash.

SULFASALAZINE

Mechanism

5-ASA derivative. Decreases inflammatory response in the colon and systemically inhibits prostaglandin synthesis.

Uses

An enteric coated tablet indicated for UC. It can also be used for rheumatoid arthritis.

Side Effects

Contraindicated in patients with sulfa allergy. Most patients experience GI intolerance upon initiation of this drug.

ONDANSETRON

Mechanism

Antiemetic selective serotonin ($5\text{-}HT_3$) receptor antagonist. Blocks serotonin on peripheral vagal nerve terminals and in the central chemoreceptor trigger zone.

Uses

Prophylaxis for highly emetogenic chemotherapy and for prevention and treatment of postoperative nausea and vomiting.

Side Effects

Should be used on a scheduled basis for chemotherapy, not as needed because it is indicated for the prevention of nausea. Side effects include headaches, malaise, and constipation.

TABLE 3-20. Consequences of Antacid Overuse

Aluminum-containing antacids	▪ Constipation. ▪ Binds to tetracycline to form insoluble complex that is not absorbed. ▪ Increases absorption of certain drugs such as levodopa. ▪ Antacid binds to secreted and ingested phosphate to form insoluble salts; hypophosphatemia may lead to osteomalacia and myopathy.
Sodium-containing antacids	▪ Transient metabolic alkalosis. ▪ Fluid retention. ▪ Hypernatremia.
Magnesium-containing antacids	▪ Hypermagnesemia, fluid and electrolyte imbalance. ▪ Hypophosphatemia. ▪ Diarrhea.
Calcium-containing antacids	▪ Milk-alkali syndrome may lead to hypercalcemia and metabolic alkalosis. ▪ Constipation.

ANTACIDS

Antacids are weak bases that decrease gastric acidity by neutralizing gastric acid to form water and a salt. They also affect the action of pepsin, which requires a pH < 4.0. Agents are composed of sodium bicarbonate and aluminum, magnesium, or calcium salts. Aluminum and magnesium salts are most common and promote the healing of duodenal ulcers. Chronic use of antacids, however, may lead to unwanted effects (see Table 3-20).

Rapid Review

Key Terms

Anasarca	Generalized (whole body) edema.
Cirrhosis	End stage of chronic liver disease defined histologically by bridging fibrous septa, parenchymal nodules, and disruption of the entire liver architecture.
Cholestasis	Retention of bilirubin and other solutes eliminated in bile due to hepatic dysfunction or biliary obstruction. Associated with pruritus and elevated serum alkaline phosphatase.
Choledocholithiasis	Gallstones in the biliary tree. May cause pancreatitis, cholangitis, hepatic abscess, chronic liver disease, or acute calculous cholecystitis due to biliary obstruction.
Dysphagia	Difficulty in swallowing.
Heartburn	Retrosternal burning due to reflux of gastric contents into the esophagus.
Hematemesis	Vomiting blood. This can signal eruption of esophageal varices.
Hypochlorhydria/ achlorhydria	Decreased HCl production, and no HCl production, respectively.
Keratoconjunctivitis	Dry eyes.
Melena	Dark tarry stools secondary to digested blood.
Pruritus	Generalized itching.
Tenesmus	Sensation of rectal sphincter spasm.
Xerostomia	Dry mouth.

TABLE 3-21. Congenital Abnormalities

Meckel's diverticulum	*Failure of the omphalomesenteric duct to involute, leaving a persistent* blind-ended tubular protrusion along the small bowel. Remember the rule of **2s: 2** feet from the ileocecal valve, **2** inches in length, affects **2%** of the population, **twice** as common in males, and can contain **two** types of tissue (stomach or pancreas).
Omphalocele	Defect of the periumbilical abdominal wall allowing protrusion of a membranous sac of peritoneum into which the intestines herniate. The defect is midline. Associated with other congenital malformations.
Gastroschisis	Defect of the abdominal wall lateral of midline that is not covered with peritoneum. Usually an isolated congenital defect.
Malrotation	Abnormality in development causing the intestines to take a different position in the abdomen than usual.
Intussusception	Telescoping of a proximal segment of bowel into a distal segment. In adults, such telescoping often points to an intraluminal mass (tumor).
Volvulus	Twisting of a loop of bowel or other structure about its base of attachment, constricting venous outflow. The large intestine is predisposed to volvulus.
Biliary atresia	Complete obstruction of bile flow caused by destruction or absence of the extrahepatic bile ducts. An acquired inflammatory disorder of unknown cause which can present as neonatal cholestasis.
Hirschsprung's disease	An aganglionic segment of defunctionalized large bowel due to failure of migration of neural crest cells during organogenesis. Presents in infants as failure to pass meconium in the first few days after birth. **Meissner's plexus** controls secretions and blood flow. **Auerbach's plexus** controls smooth muscle motility.

Congenital abnormalities are listed in Table 3-21, respectively.

ACHALASIA

Incomplete relaxation of the LES in response to swallowing. Can lead to SCC of the esophagus. "**Bird's beak" sign** is visible on plain films of the chest.

- **Primary achalasia:** Loss of innervation of the LES and smooth muscle (Auerbach's plexus).
- **Secondary achalasia:** Pathologic process that impairs esophageal motility.

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Injury to the esophagus with subsequent inflammation attributed to decreased resting tone of the LES. Clinically presents as heartburn and can mimic a heart attack. May be seen with hiatal hernias. Predisposes to Barrett's esophagus. Three histologic features are characteristic of reflux esophagitis:

- Eosinophils on biopsy (if more serious, neutrophils as well) > 15 eosinophils/HPF.
- Basal zone hyperplasia.
- Elongation of the lamina propria papillae (papillary fingers).

Barrett's Esophagus

A complication of long-standing gastroesophageal reflux defined as the replacement of the normal stratified squamous mucosa by metaplastic columnar epithelium containing goblet cells. This is most common in white males and can lead to the development of adenocarcinoma.

HIATAL HERNIAS

Herniation of part of the stomach into the thoracic cavity. Associated conditions include reflux, ulceration, bleeding, and perforation.

- **Sliding hernia (95%):** Protrusion of the stomach above the diaphragm, creating a bell-shaped dilation. GERD may be a manifestation.
- **Paraesophageal hernia:** Part of the greater curvature protrudes through the esophageal hiatus, next to the esophagus. More prone to strangulation than a sliding hernia. Not a surgical emergency, but should be repaired once discovered.

ESOPHAGEAL CARCINOMA

Presents with dysphagia, odynophagia, and obstruction. Two main forms are recognized:

Squamous Cell Carcinoma

More common in blacks than whites. Predisposing factors include slow transit of food through the esophagus and smoking or drinking. Most common esophageal cancer worldwide.

Adenocarcinoma

Primary form in the United States. Barrett's esophagus is the only known precursor to adenocarcinoma. Usually found in the distal one-third of the esophagus and can invade the esophageal wall, stomach, or other local structures. Associated with GERD.

MALLORY-WEISS TEAR

Longitudinal tears in the esophagus at the esophagogastric junction. Associated with severe retching (alcohol intoxication). Accounts for 5%–10% of upper GI bleeds.

Boerhaave's Syndrome

Rare. Occurs in the setting of spontaneous esophageal rupture with exit of gastric contents into the mediastinum. Associated with overindulgence in food and alcohol. High mortality rate.

GASTRITIS

Inflammation of the gastric mucosa. May present with a variety of nonspecific upper GI symptoms (nausea, bloating, and reflux) and even upper GI bleed-

ing. Diagnosed with upper endoscopy (esophagogastroduodenoscopy). Clues to differentiation of its etiology include a thorough medication history, time course, and clinical situation.

Acute Gastritis

Acute mucosal inflammatory process, usually of a transient nature. Frequently associated with NSAIDs, chemical ingestion, excessive alcohol and tobacco consumption, and trauma. Major cause of hematemesis, particularly in alcoholics.

- **Acute erosive gastritis:** Acute gastritis with concurrent erosion and hemorrhage of the mucosa.

Chronic Gastritis

The presence of chronic mucosal inflammatory changes leading to mucosal atrophy and epithelial metaplasia. Lymphocytic and plasma cell infiltrates are seen in the lamina propria (possibly with gland loss and mucosal atrophy).

Autoimmune Gastritis

Results from autoantibodies that target the gastric gland parietal cells; specifically, the acid-producing enzyme H,K-ATPase. Ultimately leads to deficiency in IF and pernicious anemia.

PEPTIC ULCER DISEASE

Round, sharply punched-out craters found along the lesser curvature of the stomach or proximal duodenum. Caused by mucosal exposure to gastric acid/pepsin and *Helicobacter pylori* infection. Unlike ulcerated cancers, there is no significant elevation or beading of the edges. Diagnosis is made by upper endoscopy. *H. pylori* is diagnosed via biopsy, serum serology, stool antigen, or urea breath test. After treatment, do **not** attempt to confirm eradication with serology; it will always be positive.

- **Presentation:** Burning epigastric pain that may radiate to the back and is relieved by antacids. Pain may be aggravated by food (gastric ulcers) or relieved by food (duodenal ulcers).
- **Complications:** Ulcer perforation may cause peritonitis and is a surgical emergency.

Zollinger-Ellison's Syndrome

This syndrome is associated with multiple peptic ulcerations in the stomach and duodenum due to excess gastrin secretion by a gastrinoma, leading to excess gastric acid production.

Curling's Ulcers

Ulcers in the presence of severe burns.

Cushing's Ulcers

Ulcers in the presence of CNS injury.

GASTRIC CANCER

Most often found along the lesser curvature in the pylorus and antrum region. Clinical outcome is related to **depth** of invasion. In early gastric carcinoma,

TABLE 3-22. Other GI Tumors

GI stromal tumor	Neoplasm of the small intestine with a *KIT* (tyrosine kinase receptor) mutation. Treated with the tyrosine kinase receptor inhibitor imatinib, which was originally developed for treatment of chronic myeloid leukemia.
Carcinoid tumor	Small, slow-growing neoplasm arising from neuroendocrine cells along the GI tract. Secretes vasoactive hormones, creating a carcinoid syndrome **(wheezing, flushing, diarrhea, and right-sided valvular lesions)**. Associated with elevated **5-HIAA** levels. May occur in the stomach, small bowel, appendix, colon, rectum, or lung. The clinical manifestations of carcinoid syndrome appear upon metastasis to the liver.
MALT lymphoma (MALToma)	Lymphoma arising from MALT B cells. Usually affects adults and may arise anywhere in the gut (mostly the stomach and small intestine). Most MALT lymphomas are sporadic. Associated with ***Helicobacter pylori.***

the tumor is confined to the mucosa and submucosa and may exhibit a flat or excavated appearance. Advanced gastric carcinoma extends into the muscularis propria and beyond. There are two morphological types:

- **Intestinal:** Malignant cells form neoplastic intestinal glands resembling those of colonic adenocarcinoma.
- **Diffuse:** Composed of gastric-type mucous cells that do not form glands but permeate the mucosal wall as scattered "signet-ring" cells. Has red, mucin-containing tumor cells.

Linitis Plastica (Leather Bottle Stomach)

Term applied to a stomach whose gastric wall is extensively infiltrated by malignancy.

Krukenberg's Tumor

Metastatic spread of gastric cancer to both ovaries (see Table 3-22).

INFLAMMATORY BOWEL DISEASE (IBD)

Chronic intermittent disorders of unknown origin thought to be due to genetic predisposition and environmental insult. Common symptoms at presentation include **crampy abdominal pain, diarrhea** with **blood** or **mucus**, weight loss, tenesmus, and a host of symptoms outside the GI system.

Crohn's Disease (CD)

CD can involve any portion of the GI tract from the mouth to the anus (most commonly the terminal ileum). It is characterized by **transmural** involvement of the bowel wall, **noncaseating granulomas**, and fistula formation. Other common findings include:

- **Creeping fat**
- **String sign**
- **Skip lesion** (can occur in patches, unlike UC, which is continuous)
- **Crypt abscesses**

Ulcerative Colitis (UC)

UC involves the **large intestine** starting at the rectum and moving proximally in a **continuous fashion**. Unlike CD, it is limited to the **mucosa and submucosa**. Associated with an **increased risk of colon cancer**.

- **Pseudopolyps:** Isolated islands of regenerating mucosa that bulge upward.

COLONIC POLYPS

Colonic polyps can be malignant or benign, hereditary or spontaneous. The key to differentiation will be the patient presentation, age, family history, and associated symptoms (see Table 3-23).

COLONIC ADENOMAS

Neoplastic polyps that range from small, pedunculated tumors to large sessile lesions. There are three subtypes. In terms of risk of malignant transformation villous > tubulovillous > tubular.

- **Tubular adenoma:** Most common. Usually arise in the rectosigmoid part of the colon. Histologically, the stalk is covered by normal mucosa, but the head is composed of neoplastic epithelium.
- **Villous adenoma:** Up to 10 cm in diameter, velvety or cauliflower masses projecting 1–3 cm above the normal mucosa.
- **Tubulovillous adenoma:** Composed of a mix of tubular and villous areas.

Colorectal Cancer

Adenocarcinomas make up 98% of all cancers in the large intestine. The peak incidence is 60–70 years of age. When found in a young person, think of UC or another polyposis syndrome. Adenomas are the presumed precursor lesion.

TABLE 3-23. Types of Colonic Polyps

Cowden's syndrome	Hamartomatous polyps in the GI tract. Increased risk of neoplasms of the thyroid, breast, uterus, and skin.
Familial adenomatous polyposis (FAP)	Patients develop 500–2500 colonic adenomas that carpet the mucosal surface. Most polyps are tubular adenomas. 100% risk of colonic cancer by midlife. Increased risk of duodenal cancer.
Gardner's syndrome and Turcot's syndrome	Both of these syndromes share the same APC genetic defect as FAP, but differ in one regard: these two syndromes have extraintestinal tumors whereas FAP does not.
Hyperplastic polyp	No malignant potential. Formed as the result of abnormal mucosal *maturation, inflammation, or architecture.*
Juvenile polyp	Hamartomatous proliferations of the lamina propria enclosing widely spaced, dilated cystic glands. Usually seen in children < 5 y.
Peutz-Jeghers' syndrome	Hamartomatous polyps and melanotic mucosal and cutaneous pigmentation.

CEA is a serum marker for disease, but is of little diagnostic value for colon cancer since it may also be elevated in other conditions.

APPENDICITIS

Inflammation of the appendix secondary to obstruction. Classical presentation is mild periumbilical discomfort that migrates to the right lower quadrant with tenderness at **McBurney's point** (one-third of the way up a line drawn between the anterior superior iliac spine and the umbilicus). Associated with anorexia, nausea, and vomiting.

DIARRHEA

Acutely defined as an increase in the number of stools with a loose consistency of less than 30 days duration. Diarrhea lasting longer than 30 days is considered chronic. The presence or absence of blood is an important component of the history. Common laboratory studies to aid in diagnosis include fecal leukocytes and culture, stool fat content, ova and parasites, and *Clostridium difficile* toxin.

Typhoid Fever

Salmonella typhi is the agent responsible for typhoid fever. Involves bacteremia, splenomegaly, and even liver necrosis, as well as ulceration of Peyer's patches with intestinal bleeding and ulceration. If the gallbladder is colonized, the individual becomes a carrier. Causes **rose spots** (classic rash on the skin).

Pseudomembranous Colitis

C. difficile is a part of the normal flora of the bowel, but with antibiotic use can overgrow producing a cytotoxin (pseudomembrane). A distinctive pseudomembranous colitis is produced which if not recognized can lead to toxic megacolon.

Entamoeba histolytica

E. histolytica is a dysentery-causing protozoan parasite. Amebae invade the crypts of colonic glands and burrow down into the submucosa. The organisms fan out laterally creating **flask-shaped ulcers**. They can penetrate the portal venous system and spread to the liver causing abscesses. Diagnosis is by stool ova and parasites or stool *E. histolytica* antigen.

Giardia lamblia

G. lamblia is an intestinal protozoan that attaches to the small intestinal mucosa but does not appear to invade. Therefore, fecal leukocyte tests are negative. Associated with greasy, fatty stools and foul-smelling flatulence. Diagnosis is by *Giardia* antigen stool testing. Treatment is metronidazole.

Cryptosporidia

Cryptosporidiosis leads to diarrhea in immunocompromised people and is a potentially fatal complication of AIDS (see Table 3-24).

TABLE 3-24. Causes of Diarrhea

Causes of Bloody Diarrhea	Causes of Watery Diarrhea
Campylobacter	*Vibrio cholerae*
Salmonella	*Clostridium perfringens*
Shigella	*Giardia*
Enterohemorrhagic *Escherichia coli* (EHEC)	*Cryptosporidium* (in immunocompromised)
Enteroinvasive *E. coli* (EIEC)	Enterotoxigenic *E. coli* (ETEC)
Yersinia	Viruses (rotavirus, Norwalk, adenovirus)
C. difficile	
Entamoeba histolytica	

MALABSORPTIVE SYNDROMES

May present with large-volume, fatty, bulky, foul-smelling stools. Associated symptoms include bloating and weight loss despite adequate food intake. Patients are subject to malnutrition given failure to absorb nutrients.

Lactose Intolerance

Inability to digest lactose, causing an osmotic diarrhea. Lactose intolerance can be inherited (deficiency of disaccharidase; rare) or acquired. In infants, the disease can lead to diarrhea, weight loss, and failure to thrive.

Celiac Disease

Noninfectious cause of malabsorption resulting from a reduction in small intestinal absorptive surface area. The basic disorder in celiac disease is sensitivity to gluten, the component of wheat and related grains that contains the water-insoluble protein gliadin. Villous atrophy in the small intestine is the histologic hallmark of the disease, along with transglutaminase, and endomysial and anti-gliadin antibodies.

Whipple's Disease

Whipple disease is a rare, systemic infection (*Tropheryma whippelii*) that may involve any organ of the body, but principally affects the intestine, CNS, and joints. The hallmark of Whipple's disease is PAS-positive macrophages in the lamina propria of the small intestine. The effects of this disease are felt as a malabsorptive syndrome occasionally accompanied by lymphadenopathy.

DIVERTICULAR DISEASE

A blind pouch (diverticulum) in the colon leading off the alimentary tract, lined by mucosa that communicates with the lumen of the gut. A common disease, its incidence increases with age. May present as an asymptomatic finding on colonoscopy or from complications (lower GI bleeding or diverticulitis).

Diverticulosis

A diverticulum may erode into a blood vessel and cause lower GI bleeding. Diverticular disease is most frequently found in the sigmoid colon. Diverticulosis is the condition of having diverticula.

Diverticulitis

Infection of a diverticulum. Can present as lower abdominal pain and fevers, most frequently in the LLQ. Can lead to microperforation, abscess, and peritonitis.

MESENTERIC ISCHEMIA

Impaired blood flow to the intestines usually results from the occlusion of an artery, either secondary to peripheral vascular disease or thromboembolic events. Its extent is associated with which artery and which branch of that artery is affected. The severity ranges from transmural infarction (all layers), to mural infarction (mucosa and submucosa), and mucosal infarction. It is a surgical emergency, and presents with pain out of proportion to findings on examination.

ANGIODYSPLASIA/ARTERIOVENOUS MALFORMATION

Tortuous dilations of submucosal and mucosal blood vessels are seen most often in the cecum or right colon, usually only after the sixth decade of life. These lesions account for 20% of lower GI bleeding.

HEMORRHOIDS

Variceal dilations of the anal and perianal submucosal venous plexuses. May present with anal pain or pruritus or painless lower GI bleeding.

- **Internal:** Varicosities in the superior and middle hemorrhoidal veins appear above the anorectal line and are covered by rectal mucosa. **Painless** (visceral innervation) bleeding.
- **External:** Varicosities that appear below the anorectal line are dilations of the inferior hemorrhoidal plexus and are covered by anal mucosa. **Painful** (cutaneous innervation) with itching.

UPPER GI BLEEDING

Typically presents with **hematemesis** and **melena**. Can also present with bright red blood per rectum, but requires a very brisk bleed in this case. Upper GI bleeds can cause significant bleeding associated with hemodynamic instability. Causes include:

- **PUD:** Most common cause of upper GI bleeding.
- **Mallory-Weiss tear.**
- **Esophageal varices.**
- **Erosive gastritis/esophagitis.**
- **Dieulafoy's lesion.**
- **Aortoenteric fistula.**

LOWER GI BLEEDING

Typically presents with bright red blood per rectum (BRBPR) or melena (black tarry stools) and is foul smelling. Causes include:

- **Ischemic bowel disease.**
- **Diverticulosis.**
- **Arteriovenous malformation.**
- **Colon carcinoma.**

- Hemorrhoids.
- *Infectious colitis.*
- IBD and UC.

HERNIA

A weakness or defect in the wall of the peritoneal cavity may permit protrusion of a pouch-like, serosa-lined sac of peritoneum called a hernial sac. Pressure at the neck of the pouch may impair venous drainage of the trapped viscus. Stasis and edema ensue leading to permanent entrapment of the herniated loop (incarceration). Further compromise of blood supply leads to infarction (strangulation). These may include inguinal (direct and indirect), femoral, obturator, ventral, umbilical, and incisional, as well as esophageal, diaphragmatic, and even internal.

ADHESION

Adhesions may occur between bowel segments and the abdominal wall. They are fibrous bridges that that can create closed loops through which intestines may slide and become trapped (causing internal herniations). Frequently occur as a result of intra-abdominal surgery.

PANCREATITIS

Acute Pancreatitis

Characterized by acute onset of abdominal pain resulting from enzymatic necrosis and inflammation of the pancreas with an accompanying elevation of pancreatic enzymes (**lipase and amylase**) in the blood and urine. Two main causes in the United States include **alcoholism** and **gallstones.** Also occurs as a complication following ERCP.

- **Associations.** Hypocalcemia (secondary to the precipitation of calcium salts in the peritoneal cavity) and **ARDS**.
- **Pancreatic pseudocyst.** A common sequela of acute pancreatitis defined as a liquefied area of necrotic pancreatic tissue that is walled off by fibrous tissue to form a cystic space, which does not contain an epithelial lining.

Chronic Pancreatitis

Characterized by repeated bouts of mild to moderate pancreatic inflammation with continued loss of pancreatic parenchyma and replacement by fibrous tissue. Can present as mild to severe abdominal pain with only a slight increase in pancreatic enzymes. Most frequently occurs in middle-aged alcoholic men.

- *CFTR* **gene:** Mutation is found in approximately one-third of people with chronic pancreatitis.
- **Complications:** May lead to the development of DM and severe chronic pain and malabsorption.

PANCREATIC CARCINOMA

Carcinoma arising from the exocrine portion of the pancreas. Less than 5% of people with pancreatic cancer will live beyond 5 years. These are almost always adenocarcinomas and tend to present fairly late in the course. Usually arise in the head of the pancreas, causing biliary obstruction leading to

painless jaundice, and known as **Courvoisier's sign** (**a palpable distended gallbladder**).

- *K-RAS* and *CDKN2A*: Most common gene mutations in pancreatic carcinoma. Considered a "molecular fingerprint" for pancreatic cancer.
- **Trousseau's syndrome:** Spontaneously appearing phlebothrombosis or migratory thrombophlebitis.
- CA19-9: Serum antigen that has been found to be elevated in carcinoma of the pancreas.

ISLET CELL TUMORS

Originate in neuroendocrine cells (and thus resemble carcinoids) and have a propensity to elaborate pancreatic hormones (see Table 3-25).

INBORN ERRORS OF BILIRUBIN METABOLISM

Elevated Unconjugated Bilirubin

Crigler-Najjar's Syndrome (Type 1)

Rare autosomal recessive condition with a complete lack of the enzyme responsible for conjugating glucuronic acid to bilirubin.

- **Kernicterus:** Associated with diffusion of unconjugated bilirubin into brain tissue (namely the basal ganglia) resulting in toxic damage and death.

Crigler-Najjar's Syndrome (Type 2)

Partial defect in the conjugating enzyme.

Gilbert's Syndrome

Present in up to 7% of the population. The syndrome is caused by decreased levels of glucuronosyltransferase, causing mild, fluctuating unconjugated hyperbilirubinemia.

TABLE 3-25. Types of Islet Cell Tumors

Insulinomas	Rare. Cause fasting hypoglycemia and may present with palpitations, tremulousness, and mental status changes.
Gastrinoma	Clinically causes Zollinger-Ellison's syndrome due to hypergastrinemia. Marked hypersecretion of gastrin. Locally invasive tumors that have usually metastasized by the time of diagnosis. Arise not only in the pancreas, but also in the duodenum and peripancreatic tissues as well.
Glucagonoma	Presents with weight loss and a picture similar to that of diabetes mellitus. Rare.
Somatostatinoma and VIPoma	Exceedingly rare. VIPoma causes watery diarrhea.

Elevated Conjugated Bilirubin

Dubin-Johnson's Syndrome

Results from an autosomal recessive defect in the transport protein responsible for hepatocellular excretion of bilirubin glucuronides across the canalicular membrane. The liver is pigmented and often enlarged, but is functionally normal.

- **Rotor's syndrome:** Variant of Dubin-Johnson's syndrome in which the liver is not pigmented.

CIRRHOSIS

Cirrhosis is the end stage of chronic liver disease defined by bridging fibrous septa, parenchymal nodules, and disruption of the entire liver architecture. A patient with cirrhosis will present with signs and symptoms associated with portal hypertension and hyperestrogenemia (see Table 3-26).

Esophageal Varices

Dilated veins in the distal esophagus which can rupture and cause significant blood loss. Esophageal veins are sites of communication between portal veins and systemic veins. When portal venous flow is obstructed, portal hypertension shunts blood to these veins and causes dilation of vessels. Associated with alcoholic cirrhosis.

HEPATITIS

Injury to hepatocytes associated with an influx of acute or chronic inflammatory cells into the liver is termed hepatitis. Causes include viral, autoimmune, and metabolic. Associated with **jaundice**, a yellow discoloration of skin and sclerae (icterus) that occurs when systemic retention of bilirubin leads to elevated serum levels above 2.0 mg/dL. Most frequently caused by hemolytic anemias (elevated unconjugated bilirubin), hepatitis, and obstruction of the flow of bile. Presents with jaundice and elevated AST and ALT.

TABLE 3-26. Cirrhosis of the Liver

Symptoms of Portal Hypertension	Symptoms of Hyperestrogenemia
Ascites.	Palmar erythema.
Portosystemic venous shunts. Esophageal varices, caput medusae, and hemorrhoidal veins.	Spider angiomas.
Congestive splenomegaly.	Hypogonadism (testicular atrophy).
Hepatic encephalopathy. Can cause fetor hepaticus (a musty body odor), **asterixis** (nonrhythmic, rapid extension-flexion movements of the hands and tongue). Hepatorenal syndrome.	Gynecomastia in males.

Hepatitis A

Benign, self-limited disease that does not cause chronic hepatitis or a carrier state. Rarely causes fulminant hepatitis. Spread by ingestion of contaminated water or food or raw or steamed shellfish.

Hepatitis B

Major cause of liver disease. Can produce acute hepatitis, progressive and nonprogressive chronic hepatitis, fulminant hepatitis with massive liver necrosis, and an asymptomatic carrier state. Found in all body fluids except the stool. Can be spread by needlesticks or as an STD, as well as vertically from mother to child.

Hepatitis C

Major cause of liver disease. Major routes of transmission are inoculations and blood transfusions and IV drug use. Occupational exposure to health care workers accounts for 4% of cases in the United States. Hepatitis C has a higher rate of progression to chronic disease and eventual cirrhosis than hepatitis B. Concurrent HCV infection with alcoholic liver disease accelerates the course of liver disease.

Hepatitis D

HDV needs to be encapsulated in HBsAg to be infective, thus HDV is absolutely dependent on HBV coinfection for multiplication. In the United States, HDV infection is mostly restricted to IV drug abusers.

Hepatitis E

HEV is an enterically transmitted, water-borne infection seen mainly in travelers. A characteristic feature of HEV is the high mortality rate among **pregnant women**.

Autoimmune Hepatitis

Syndrome of chronic hepatitis in patients with a set of immunologic abnormalities. Salient features include female preponderance, presence of other autoimmune diseases, and an increase in serum IgG. There are three types of autoimmune hepatitis grouped according to the target of the autoantibodies, most commonly associated with **anti–smooth muscle antibodies (ASMA)**, and **anti-nuclear antibodies (ANA)**.

ALCOHOLIC LIVER DISEASE

Alcohol is the leading cause of liver disease in most Western countries. There are three components to alcoholic liver disease: hepatic steatosis, alcoholic hepatitis, and cirrhosis. The AST:ALT ratio may often be 2:1 in frequent drinkers.

- **Hepatic steatosis.** Lipid droplets accumulate in hepatocytes giving the liver a fatty appearance. Up to the time that fibrosis appears, the fatty change is completely reversible if patient abstains from alcohol.
- **Alcoholic hepatitis.** This is characterized by hepatocyte swelling and necrosis, **Mallory bodies** (eosinophilic cytoplasmic hyaline inclusions in degenerating hepatocytes), neutrophilic reaction, and fibrosis.
- **Alcoholic cirrhosis.** Final and irreversible form. The liver progresses from being large and fatty to a brown, shrunken organ. In time, micronodules form from regenerating hepatocytes trapped between the fibrotic strands.

Eventually, the nodules predominate and vary in size, creating a hobnail appearance.

Nonalcoholic Fatty Liver (NAFL)

This is fatty liver occurring in patients who do not drink alcohol. The single most consistent association for NAFL is **obesity** and/or type 2 diabetes mellitus. NAFL is diagnosed on liver biopsy and is often under-recognized.

Nonalcoholic Steatohepatitis (NASH)

The presence of parenchymal mixed inflammation with neutrophils and mononuclear cells, hepatocytes containing Mallory hyaline, and hepatocyte destruction earns the moniker nonalcoholic steatohepatitis.

PRIMARY BILIARY CIRRHOSIS

Chronic, progressive, and often fatal autoimmune cholestatic liver disease. Characterized by the destruction of intrahepatic bile ducts, portal inflammation and scarring, and liver failure. Associated with **antimitochondrial antibody** in over 90% of patients. Usually affects women between 40 and 50 years, and can be associated with autoimmune disease (i.e., Sjögren's syndrome, scleroderma, or Raynaud's syndrome).

LIVER ABSCESS

Most common in developing countries due to parasitic (amebic) infections. In developing countries, the cause is more often bacterial or fungal, representing a complication of an infection elsewhere. Liver abscesses are associated with fever, and often right upper quadrant pain and tender hepatomegaly.

INBORN ERRORS OF METABOLISM

Hereditary Hemochromatosis

Excessive accumulation of body iron, most of which is deposited in the parenchymal organs such as the liver and pancreas. Normal levels of iron are 2–6 grams, while hemochromatosis is associated with levels of 50 grams or higher. Affects males > females, rarely seen before age 40. Principal manifestations are hepatosplenomegaly, abdominal pain, skin pigmentation, DM (hence the term "**bronze diabetes**") from destruction of pancreatic islets, cardiac dysrhythmia, and atypical arthritis. May predispose to HCC. Genes associated with the disease are the ***HFE* gene/C282Y/C282Y**, and an ***H63D*/C282Y** mutation.

Wilson's Disease

Autosomal recessive disorder of copper metabolism that is marked by the accumulation of toxic levels of copper in many tissues and organs, principally the liver, brain, and eye. Defective transporter fails to secrete copper from the liver into the bile. Clinically manifests with **Kayser–Fleischer rings** (eye lesions that are green to brown deposits of copper in the Descement membrane in the limbus of the cornea) and low **ceruloplasmin** (hepatocellular uptake of copper followed by incorporation of α-globulin forms ceruloplasmin, which is then secreted into the blood). May also present with neuropsychological symptoms. Rarely appears before 6 years of age.

α_1-Antitrypsin Deficiency (AAT)

Autosomal recessive disorder marked by abnormally low serum levels of the protease inhibitor α_1-antitrypsin. Those with AAT deficiency have a **PiZZ** genotype. AAT is synthesized in the liver. Those with the deficient allele form a mutant AAT that is not released by the liver; therefore, there is an accumulation of AAT which can cause cholestasis and liver damage. Can also cause hepatitis and COPD-like pulmonary disease.

REYE'S SYNDROME

This is a rare disease characterized by fatty change in the liver and encephalopathy. Primarily affects children under 4 years, typically following a viral infection. Presents with pernicious vomiting and irritability, lethargy, and hepatomegaly. Associated with the administration of **aspirin** to children during viral infections.

HEPATIC VEIN THROMBOSIS (BUDD–CHIARI SYNDROME)

Acute, subacute, or chronic occlusive syndrome of the hepatic veins, characterized by hepatomegaly, weight gain, ascites, and abdominal pain. Thrombosis is most often associated with states that produce sluggish blood flow (e.g., polycythemia vera, paroxysmal nocturnal hemoglobinemia, and pregnancy). In this syndrome, the liver is often swollen, red-purple, and has a tense capsule.

HEPATOBILIARY CANCERS

Liver Cell Adenoma (Hepatoma)

Liver cell adenoma is a benign neoplasm of hepatocytes most commonly occurring in women of child-bearing age who have used **oral contraceptives**. The tumor regresses if the oral contraceptives are stopped.

Hepatocellular Carcinoma (HCC)

Primary carcinoma of the liver that most commonly arises from hepatocytes. Rare in the United States, but represents 20%–40% of cancers in other countries (incidence is linked to HBV and HCV). Most liver cancers in the United States are metastases to the liver. Exposure to dietary **aflatoxins** derived from the fungus *Aspergillus flavus* is linked to HCC. **AFP** is a serum marker that may be elevated in HCC.

Cholangiocarcinoma

Carcinoma of bile duct origin. The only known causal influences of cholangiocarcinoma are primary sclerosing cholangitis, chronic infection of the biliary tract by the liver fluke ***Opisthorchis sinensis***, choledochal cysts, and previous exposure to **Thorotrast**, which contained thorium dioxide, and was formerly used in radiography of the biliary tract. It usually appears as a well-differentiated adenocarcinoma.

CHOLELITHIASIS

Gallstones in the gallbladder. They most commonly affect middle-aged white women who are obese (also associated with oral contraceptives). A mnemonic for those most commonly affected is the 4 Fs: Fat, Fertile, Female, and Forty.

Most gallstones are asymptomatic, though they have the potential to cause constant or colicky abdominal pain and cholecystitis. Stones may be composed of either cholesterol or pigment (seen with hemolytic anemias).

CHOLECYSTITIS

Inflammation of the gallbladder that is almost always associated with gallstones. Usually associated with elevated levels of **alkaline phosphatase** and **direct (conjugated) bilirubin**. Classically presents with **Murphy's sign** (arrest of inspiration when palpating under the sternal margin in the RUQ). Predisposes to ascending cholangitis.

Acute Calculous Cholecystitis

Acute inflammation of a gallbladder that contains stones. Precipitated by obstruction of the gallbladder neck or cystic duct.

Acute Acalculous Cholecystitis

Cholecystitis without the presence of gallstones. This usually occurs in the setting of trauma, burns, a postoperative state, TPN, or sepsis. May be precipitated by dehydration and gallbladder stasis.

CHOLANGITIS

Acute inflammation of the bile duct wall, almost always caused by bacterial infection of the normally sterile lumen. Commonly occurs with choledocholithiasis. Also known as ascending cholangitis.

- **Common organisms:** *E. coli*, *Klebsiella*, *Clostridium*, *Bacteroides*, or *Enterobacter*.
- **Charcot's triad:** Classic triad of symptoms in cholangitis: fever, jaundice, and RUQ pain.
- **Reynolds' pentad:** Classic pentad of symptoms signifying more severe disease: Charcot's triad plus hypotension and mental status changes.

PRIMARY SCLEROSING CHOLANGITIS

Characterized by inflammation, obliterative fibrosis, and segmental dilation (irregular strictures and dilations) of the obstructed intrahepatic and extrahepatic bile ducts. Commonly seen in conjunction with IBD, especially UC.

PRESENTATION

Usually diagnosed in the context of IBD. May present symptomatically with abnormal liver function tests, RUQ pain, pruritus, and fatigue.

DIAGNOSIS

Cholangiography [magnetic resonance cholangiopancreatography (MRCP)] shows multiple strictures and dilation of intra- or extrahepatic bile ducts.

GALLBLADDER CARCINOMA

Tumors of the gallbladder are much more common than those arising in the bile ducts. Presents in women > men, commonly in the seventh decade of life, with 5-year survival of 1%. Gallstones are present in 60%–90% of cases. Most gallbladder carcinomas are adenocarcinomas and have typically invaded

the liver by the time of diagnosis. Risk factors: gallstone > 2.5 cm, porcelain gallbladder, and Native American or Hispanic race.

Extrahepatic Bile Duct Carcinoma

Cancers (mostly adenocarcinomas) arising in the extrahepatic ducts are extremely insidious and generally produce painless, progressively deepening jaundice. They occur in older people and slightly more often in men. Because partial or complete obstruction of bile ducts rapidly leads to jaundice, extrahepatic biliary tumors tend to be relatively small at the time of diagnosis.

- **Klatskin's tumor:** Arises at the bifurcation of the right and left hepatic ducts.

CHAPTER 4

Hematology and Oncology

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Embryology

HEMATOPOIESIS

Formation of Blood Cells

In the embryo, the outer layer of the yolk sac, derived from the extraembryonic mesoderm, is the major site for hematopoiesis. The hematopoietic stem cells migrate into the yolk sac from **primitive ectoderm** or **epiblast**. Hematopoietic stem cells leave the yolk sac and start populating the fetal **liver** between the fourth and the fifth week. After spending some time in the liver, they also migrate to other hematopoietic organs, including the spleen, lymph nodes, thymus, and bone marrow.

- **Liver:** The major site of hematopoiesis in early embryonic life.
- **Spleen:** Exclusively hematopoietic organ until 14 weeks of gestation. At around 15–18 weeks, the spleen is populated with T-cell precursors. Later, in the 23rd week, B-cell precursors enter the spleen and form B-cell regions.
- **Thymus:** Populated by the lymphocytes derived from the stem cells in the yolk sac, liver, and omentum once it is completely formed.

FLASH BACK

Binding of 2,3-bisphosphoglycerate (2,3-BPG) causes decreased affinity for O_2.
Fetal hemoglobin does not bind with 2,3-BPG, resulting in a greater affinity for O_2.

TYPES OF HEMOGLOBIN

Fetal Hemoglobin (Hbα2γ2)

Contains two alpha chains and two gamma chains. It has higher O_2 affinity than adult hemoglobin.

Adult Hemoglobin (Hbα2β2)

Contains two alpha chains and two beta chains.

FETAL CIRCULATION

Oxygenated blood enters the fetus via the umbilical vein. The oxygenated blood traveling in the umbilical vein **via the ductus venosus** (see Table 4-1 and Figure 4-1) is shunted to the IVC where it mixes with deoxygenated blood from the trunk and legs. The IVC drains into the right atrium. The **foramen ovale**, a shunt between the right atrium and the left atrium, allows the oxygenated blood from the IVC/right atrium to enter into the left atrium. High resistance in the pulmonary circuit during fetal life due to collapsed lungs causes

TABLE 4-1. Fetal Circulatory Structures and Adult Remnants

Fetal Circulatory Structures	Adult Remnants
Umbilical arteries	Medial umbilical ligaments
Left umbilical vein	Ligamentum teres hepatis
Ductus arteriosus	Ligamentum arteriosus
Ductus venosus	Ligamentum venosum
Foramen ovale	Fossa ovale

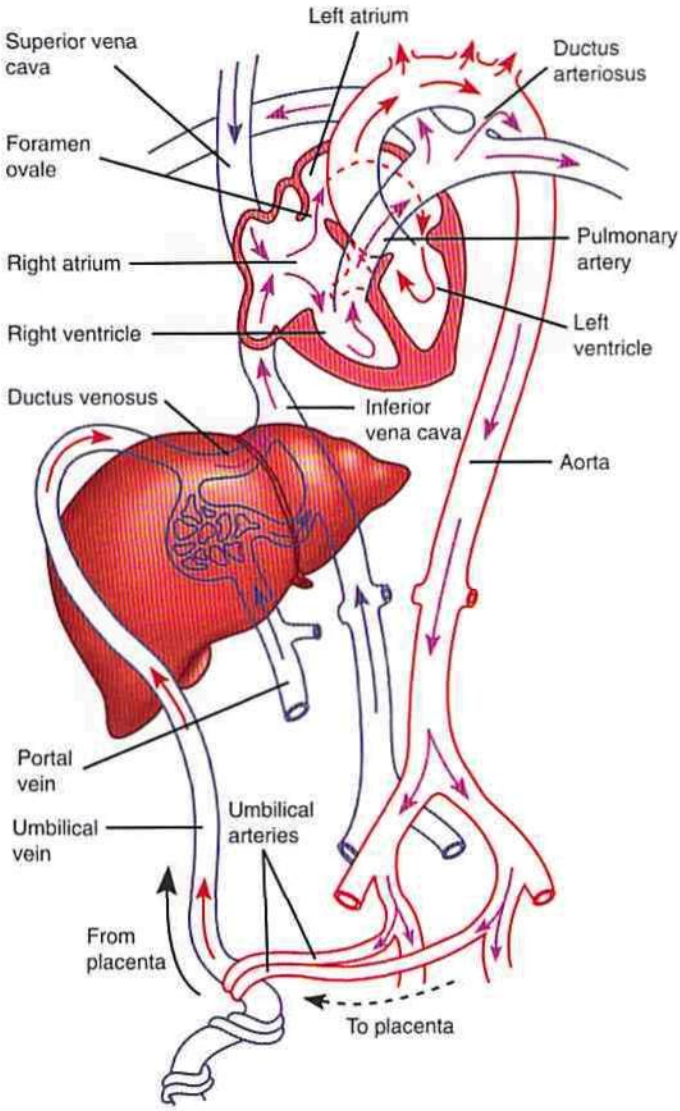


FIGURE 4-1. Fetal circulation. (Modified, with permission, from Ganong WF, *Review of Medical Physiology*, 22nd ed, New York: McGraw-Hill, 2007: 628.)

very minimal blood flow in the pulmonary circuit. Hence, a slight amount of deoxygenated blood coming from the unventilated lungs mixes with the oxygenated blood in the left atrium. The left ventricle then pumps blood (via the aortic opening) to supply the systemic circulation. At the level of the descending aorta, the **ductus arteriosus** allows for shunting of blood from the pulmonary trunk to the descending aorta. The pulmonary trunk carries deoxygenated blood from the superior vena cava and right ventricle. Finally deoxygenated blood from the lower limbs and trunk is drained by two umbilical arteries to the placenta for oxygenation.

Changes in Fetal Circulation after Birth

- Opening of the alveoli in the lungs after the first breath causes a sudden drop in pulmonary resistance.
- Increased venous return to the left atrium causes increased pressure in the heart; cessation of the umbilical blood flow causes decreased pressure in the right atrium. This change in pressure results in closure of the foramen ovale.

KEY FACT

Prostaglandins are required to keep the patent ductus arteriosus (PDA) open in the fetal period.

FLASH FORWARD

PDA is seen in congenital rubella syndrome.

FLASH FORWARD

Indomethacin is a prostaglandin inhibitor (→ decreased prostaglandin levels) and is used to close a PDA in the preterm infant.

FLASH FORWARD

Transposition of the great vessels requires either a PDA or a patent foramen ovale to allow survival of the newborn. This can be achieved by administration of prostaglandins until the condition is surgically corrected.

- Cessation of umbilical blood flow, decreased pulmonary vasculature resistance, and increased venous return to the left atrium and left ventricle result in increased flow of oxygenated blood through the ductus arteriosus. This increase in local O_2 tension causes constriction of the ductus arteriosus.

Anatomy

BLOOD

Blood is a specialized connective tissue containing RBCs, WBCs, and platelets suspended in plasma.

KEY FACT

Serum = Plasma without clotting factors.

Plasma

Plasma is yellow fluid that makes up approximately 55% of the total blood volume.

Cells

There are three major types of blood cells: erythrocytes (RBCs), leukocytes (WBCs), and platelets. Blood cells constitute about 45% of the total blood volume.

Erythrocytes (RBCs)

The erythrocyte is a biconcave, anucleated cell (see Figure 4-2) specialized to carry oxygen. It has a diameter of 7.5–8.7 μm, a volume of 90 fl, and a surface area of 136 μm^2, providing a large surface area:volume ratio. The RBC expresses different markers that can be utilized for identification as shown in Table 4-2.

KEY FACT

c5a and IL-8 are important cytokines for neutrophil chemotaxis.

RBCs exclusively utilize glucose as a source of energy, with 90% anaerobically degraded to lactate and the rest metabolized through the hexose monophosphate (HMP) shunt. They survive for 120 days and are destroyed in the spleen by macrophages.

- **Reticulocytes:** Immature RBCs that can be identified by specific staining because they contain **polyribosomes**. They account for 0.5%–1.5% of

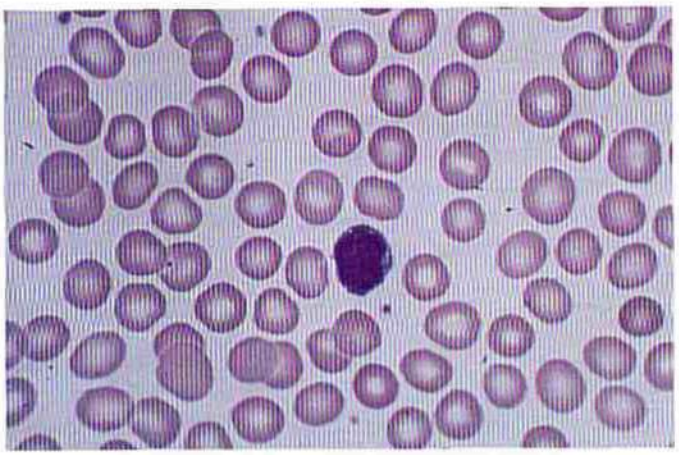


FIGURE 4-2. Anucleated, biconcave red blood cells. (Reproduced, with permission, from Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT, *Williams Hematology*, 7th ed, New York: McGraw-Hill, 2007: Plate I-1.)

TABLE 4-2. Important Red Blood Cell Markers

RBC Marker	Significance
Acetylcholinesterase	Marker for RBC aging
CD36	Expressed only by immature erythroid cells
CD47	Marker of "self" for RBCs
CD34	Expressed by early erythroid cells

RBCs. The reticulocyte count is increased in hemolytic anemia and with blood loss, and decreased in aplastic anemia or with decreased marrow production.

Leukocytes (WBCs)

Leukocytes lead the fight against infection or foreign invasion. The WBC count normally ranges from 4000 to 11,000/μL. WBCs can be divided into 5 different types of cells: neutrophils, basophils, eosinophils, monocytes, and lymphocytes.

- **Neutrophils:**
  - Neutrophils can morphologically be divided into two groups: Nonsegmented and hypersegmented.
    - **Nonsegmented** cells are immature neutrophils (also known as bands), which are seen during bacterial infections and other inflammatory conditions.
    - **Hypersegmented** neutrophils (with more than five lobes) are older cells seen in vitamin B_{12} and folate deficiencies.
  - Macrocytic anemia has many etiologies, including HIV, hypothyroidism, and alcoholism; however, only in vitamin B_{12} and folate deficiencies do hypersegmented PMNs appear on a blood smear.
  - Multilobed (3–5), phagocytic cells with granules in the cytoplasm (see Figure 4-3). They account for 60%–70% of all leukocytes and are the prime mediators of acute inflammation. Primarily two groups of granules are present in the cytoplasm, namely **specific granules** and **azurophilic granules. Specific granules** are **peroxidase negative**, small, and pale looking, while **azurophilic granules** are lysosomes that are **peroxidase positive**, large, and dense and contain myeloperoxidase enzymes. Neutrophils utilize glucose via the glycolytic pathway and have a life span of 1–4 days in blood. Neutrophils consume O_2 following phagocytosis, producing free radicals that help kill bacteria. Neutrophils also contain **lactoferrin,** which avidly binds with iron, robbing bacteria of this essential nutrient and leading to bacterial death.
- **Basophils:** Cells with bilobed nuclei (see Figure 4-3) that mediate allergic reactions. Basophils stain with basic stain (blue) and have deeply basophilic granules. Basophils account for < 0.5% of all leukocytes, and express **IgE** receptors that when triggered, release histamine, heparin, prostaglandins, leukotrienes, and other vasoactive amines. Basophils primarily **reside in blood** and have a causative role in allergic diseases including asthma and hay fever. Basophils are frequently elevated in myeloproliferative diseases.
- **Eosinophils:** Bilobed cells with large eosinophilic granules (see Figure 4-3). Eosinophils comprise 1%–6% of all leukocytes. Eosinophils function as phagocytic cells, and release cytokines and chemokines (leukotrienes,

KEY FACT

Corticosteroids inhibit polymorphonuclear neutrophil (PMN) migration from the circulation into the periphery, causing benign leukocytosis.

FLASH FORWARD

Deficiency of reduced nicotinamide adenine dinucleotide phosphate oxidase results in an increased incidence of infection with catalase-positive organisms, known as chronic granulomatous disease.

MNEMONIC

For prevalence in the blood, remember the mnemonic: Never Let Monkeys Eat Bananas.

Neutrophil
Lymphocyte
Monocyte
Eosinophil
Basophil

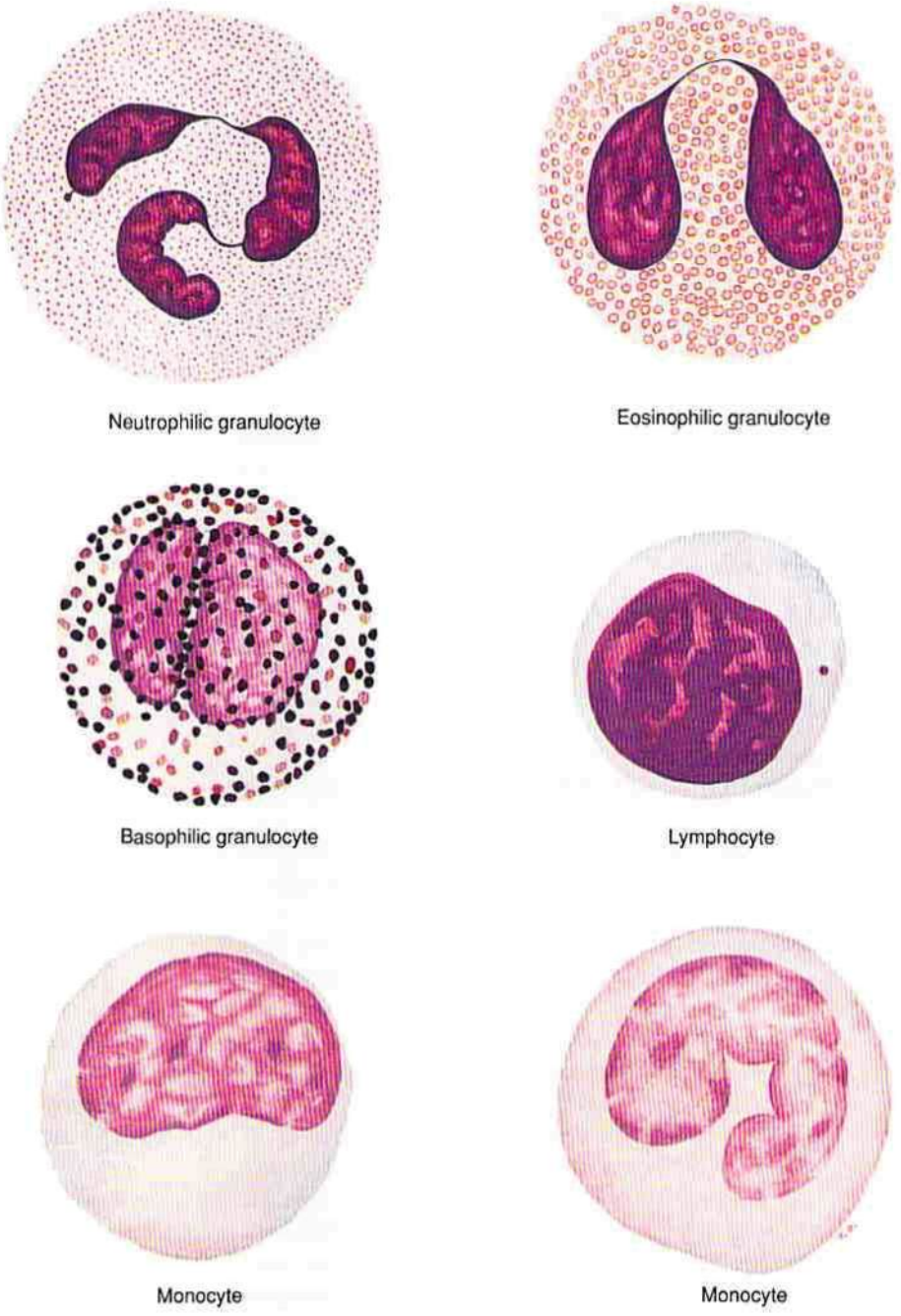


FIGURE 4-3. The five types of human leukocytes. Neutrophils, eosinophils, and basophils have granules that stain specifically with certain dyes and are called granulocytes. Lymphocytes and monocytes are agranulocytes; they may show azurophilic granules, which are also present in other leukocytes. (Reproduced, with permission, from Junqueira LC, Carneiro J, *Basic Histology: Text and Atlas*, 11th ed, New York: McGraw-Hill, 2007: 227.)

FLASH FORWARD

Cromolyn sodium is a mast cell stabilizer used to treat asthma.

MNEMONIC

Causes of eosinophilia: NAACP

Neoplasia
Asthma
Allergic processes
Collagen vascular diseases
Parasites

KEY FACT

Tartrate resistant acid phosphatase is a marker for hairy B-cell leukemia.

platelet-activating factor, prostaglandins E_1 and E_2, thromboxane B_2, histaminase, catalase, and phospholipase D), and defend against parasitic infections. Eosinophils also down regulate allergic reactions by inactivating basophil-derived histamine.

- **Monocytes:** Cells with horse-shaped nuclei (see Figure 4-3). The cytoplasm contains fine azurophilic granules (lysosomes) and appears basophilic with a "frosted-glass" appearance. Monocytes are precursor cells for macrophages and antigen-presenting cells (APCs). They account for 2%–10% of all leukocytes.

- **Lymphocytes:** Small, round cells with scant cytoplasm and densely staining nuclei (see Figure 4-3). There are four different types of lymphocytes: B cells, T cells, plasma cells, and natural killer (NK) cells. Sometimes they are also divided according to size into small, medium, and large lymphocytes.
  - **B lymphocyte:** Matures in bone marrow and migrates to peripheral lymphoid tissues (follicles of lymph nodes, white pulp of spleen, and unencapsulated lymphoid tissue). B lymphocytes mediate humoral immunity and express monomeric molecules of **IgM as the receptors for the antigen**. Recognition of the antigen leads to differentiation into plasma cells and production of antibodies (including IgG, IgA, and IgM). They function as memory cells and APCs and express MHC class II.
  - **T lymphocyte:** Matures in thymus. Precursor cells of T lymphocytes originate in the bone marrow. After maturation, T lymphocytes leave the thymus and redistribute in lymphoid tissues. They induce cell mediated immunity and express **T-cell receptor.** T lymphocytes differentiate into cytotoxic T cells (MHC I and CD 8), helper T cells (**MHC II, CD 4, and CD 43**), suppressor T cells, and delayed hypersensitivity T cells.
  - **Plasma Cell:** Eccentric cells with purple nuclei (see Figure 4-4). Cytoplasm has abundant blue rough endoplasmic reticulum and well-developed Golgi apparatus. They produce large amounts of antibodies specific for a particular antigen.
  - **Natural killer cell:** NK cells are a type of cytotoxic lymphocytes that do not express pan T-cell markers (CD3), T-cell antigen receptors, or surface Ig receptors. They express CD16 and CD56. The cytoplasm contains small granules filled with perforin and proteases that help target and kill cells lacking MHC I. This situation arises when cells are infected with viruses or tumor derived.

KEY FACT

β lymphocytes express the CD23 receptor, which Epstein–Barr virus (EBV) uses for entry into the cell.

KEY FACT

Multiple myeloma results from abnormal multiplication of plasma cells.

Macrophages

Cells with oval nuclei and blue-grey to pale cytoplasm. Macrophages serve as tissue scavengers (see Figure 4-5). They are phagocytic, consuming bacteria, aged RBCs, and cell debris. Macrophages are derived from monocytes and reside in the tissues. They also serve as APC and are activated by γ-interferon. Nitric oxide is secreted by both macrophages and the endothelium.

Dendritic Cells

Sentinels, adjuvants, and controllers of the immune system, dendritic cells also serve as APCs, and express MHC II and Fc receptors on their surface. They are the main inducers of the primary antibody response. Dendritic cells are called Langerhans cells in skin.

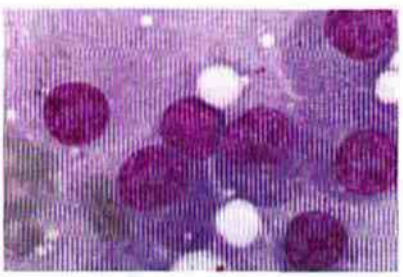


FIGURE 4-4. Plasma cells with eccentric nuclei. (Image courtesy of PEIR Digital Library [http://peir.net].)



FIGURE 4-5. Active macrophage. (Reproduced, with permission, from Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT, *Williams Hematology*, 7th ed. New York: McGraw-Hill, 2007: Plate IX-1.)

Pathology

ANEMIA

Classification and Appearance

KEY FACT

Anemia classification:
- Increased destruction versus impaired production
- Normocytic versus microcytic versus macrocytic
- Normochromic versus hypochromic

Deficiency in O_2-Carrying Capacity and/or Red Cell Mass

Anemias are classified by mechanism (increased destruction versus impaired production), red cell size (normocytic [mean corpuscular volume (MCV) 80–100], microcytic, or macrocytic), red cell shape, and hemoglobinization (normochromic vs hypochromic) (see Figures 4-6 and 4-7). Relevant signs and symptoms include weakness, fatigue, pale skin, malaise, dyspnea with exertion, koilonychias (spooning of the nails), cardiac failure, headache, and presyncope/syncope.

Acute Blood Loss

Loss of blood volume leads to a decrease in RBCs; other blood components are also affected.

Presentation

Sudden weakness, fatigue, pale skin, malaise, dyspnea, cardiac failure, headache, presyncope/syncope, and shock. Patients may have history of **trauma** or bleeding. Bleeding may be external or internal (e.g., GI losses).

KEY FACT

Corrected reticulocyte count (CRC) = Actual hematocrit/45 × Reticulocyte count. If > 3%, then a good bone marrow response to anemia is present. If it is less than 2%, then there is diminished erythropoiesis or a marrow disorder, as in iron deficiency anemia.

Diagnosis

Complete blood count (CBC), peripheral blood smear (PBS). Differential includes other anemias (especially hemolytic anemias), hypothyroidism, myelofibrosis, acute porphyria, and systemic lupus erythematosus (SLE). **Hematocrit is initially normal but decreases** as interstitial fluid shifts into the vascular compartment, causing hemodilution. **Reticulocyte count increases** as erythropoiesis peaks at around 1 week. If hemorrhage is external, iron deficiency occurs over time. Peripheral smear is **initially normochromic and normocytic**, but reticulocytes appear later as polychromatophilic macrocytes.

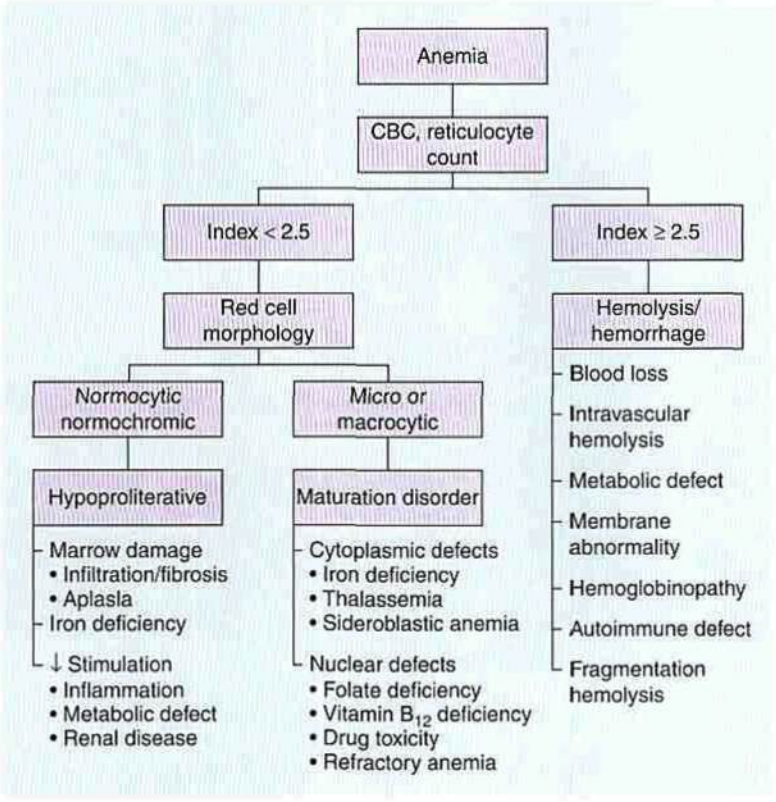


FIGURE 4-6. Classification of anemias. (Modified, with permission, from Kasper DL, Braunwald E, Fauci AS, eds, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 334.)

TREATMENT

- Fluids
- Blood transfusion
- Elimination of cause of hemorrhage
- Other measures to prevent shock

CHRONIC BLOOD LOSS

May lead to anemia when **loss exceeds erythropoiesis** or when **iron stores are diminished**. Presentation, diagnosis, treatment, and complications are similar to those of anemias caused by impaired RBC production.

Hemolytic Anemias

Result of **premature RBC destruction** causing a build-up of **hemoglobin metabolites** and an increase in **erythropoiesis**. Classified by location of destruction (intravascular versus extravascular), cause of destruction (extrinsic versus intrinsic to RBCs), and by origin of defect (hereditary versus acquired), as summarized in Table 4-3.

- **Intravascular:**
  - Due to complement fixation, mechanical injury, or toxins.
  - Look for hemoglobinemia, methemalbuminemia, mild jaundice/elevation in **unconjugated bilirubin**, hemoglobinuria, hemosiderinuria, methemoglobinuria, decreased serum haptoglobin, hemosiderosis of renal tubules, and increased fecal urobilin.

KEY FACT

Classification of hemolytic anemias:
- Location of destruction—intravascular versus extravascular
- Cause of destruction—extrinsic versus intrinsic (to RBCs)
- Origin of defect—hereditary versus acquired

KEY FACT

Intravascular→hemoglobinemia/hemoglobinuria, decreased serum haptoglobin
Extravascular→splenomegaly

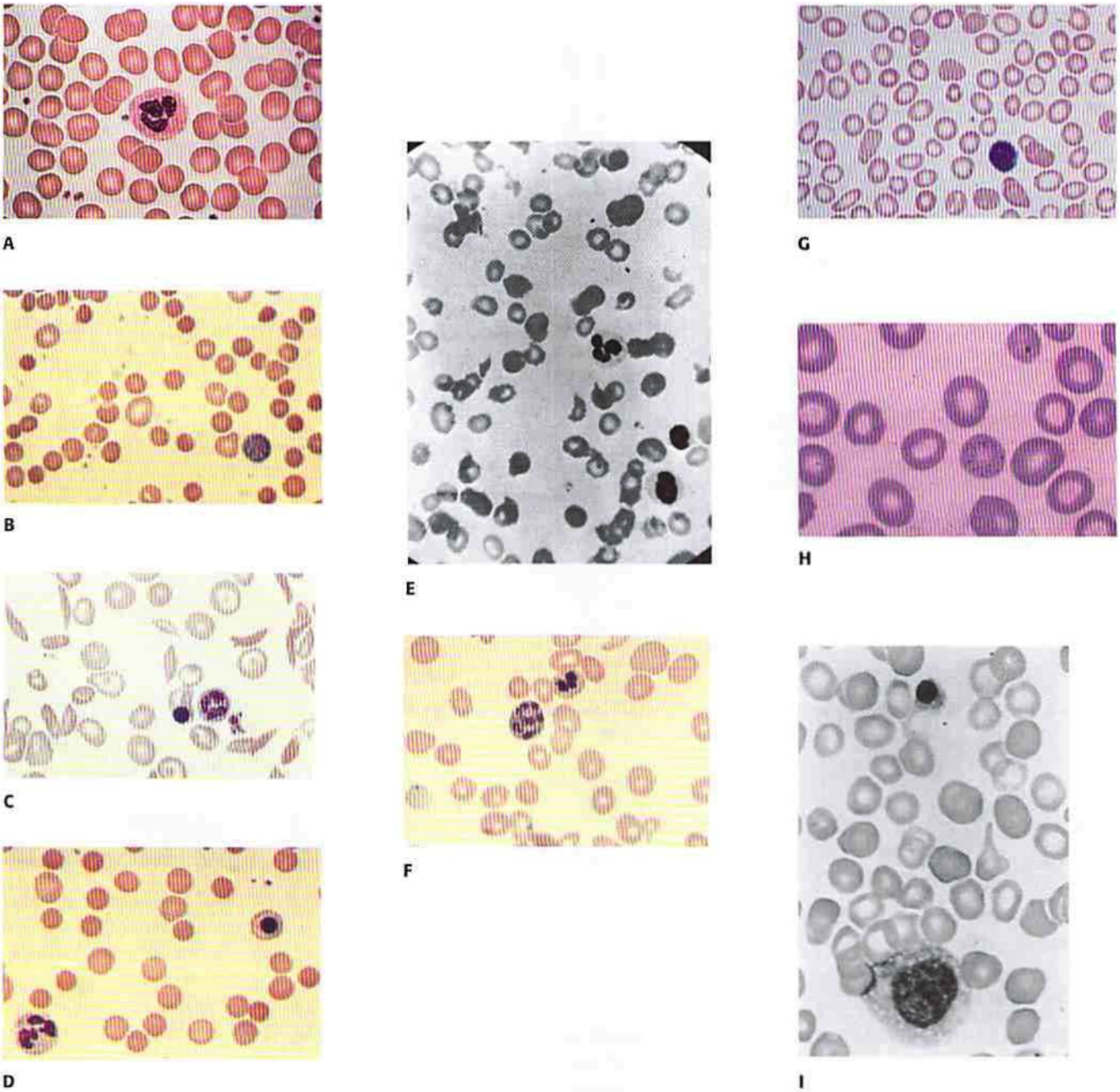


FIGURE 4-7. Anemias by appearance on peripheral blood smear. (A) Normal, no anemia: Normochromic, normocytic. (B) HS: Normochromic, normocytic, spherocytosis, reticulocytosis. (C) Sickle cell anemia: Normochromic, normocytic sickle-shaped RBCs, reticulocytosis. (D) Autoimmune hemolytic anemia: Normochromic, normocytic, spherocytosis, reticulocytosis. (E) Microangiopathic anemia or trauma to RBCs: Helmet cells, schistocytes. (F) Megaloblastic anemia: Macro-ovalocyte, macrocytic, hypersegmented neutrophils. (G) Iron deficiency anemia: Microcytic, hypochromic. (H) Lead poisoning: Microcytic, hypochromic, ringed sideroblasts. (I) Myelophthisic anemia: Nucleated RBCs and immature granulocytes. (Parts A–D & F reproduced, with permission, from Kasper DL, Braunwald E, Fauci AS, eds., *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 331, 609, 596, 613, 400; parts E & G–I reproduced, with permission, from Lichtman MA, Beutler E, Kipps TJ, et al., *Williams Hematology*, 7th ed, New York: McGraw-Hill, 2006: 450, Plate I-3, Plate IV-3, 562.)

- **Extravascular:**
  - Due to RBC injury, antibody attachment, or decrease in deformability/ability to leave cords of Billroth and enter sinusoids of spleen.
  - Hemolysis usually occurs in mononuclear phagocytic cells in spleen.
  - Look for jaundice/elevation in unconjugated bilirubin, some decrease in serum haptoglobin, and **splenomegaly**. Minimal hemoglobinemia and hemoglobinuria.

TABLE 4-3. Hemolytic Anemia

INTRINSIC	EXTRINSIC
Hereditary	**Acquired**
Enzyme deficiencies (IV and EV)	**Antibody mediated (IV)**
HMP shunt: G6PD, glutathione synthetase	Transfusion reactions
Glycolytic enzymes: pyruvate kinase, hexokinase	Erythroblastosis fetalis
Membrane disorders (EV)	Systemic lupus erythematous
Elliptocytosis	Malignant neoplasms
Spherocytosis	Mycoplasmal infection
Hemoglobin synthesis derangements (EV)	Drug-associated
Thalassemias	Idiopathic
Sickle cell anemia (can also have IV)	**Mechanical injury (IV)**
Acquired	Microangiopathic hemolytic anemias (TTP, DIC)
Membrane disorders (EV)	Cardiac traumatic hemolytic anemia
Paroxysmal nocturnal hemoglobinuria	**Infection (IV)**
	Malaria
	Chemical injury (IV)
	Lead poisoning
	Excessive destruction by spleen (EV)
	Hypersplenism

IV = intravascular; EV = extravascular.

Glucose-6-Phosphate Dehydrogenase Deficiency

In glucose-6-phosphate dehydrogenase (G6PD) deficiency, an enzyme that protects RBCs from oxidants is **abnormally folded** and subject to proteolysis in older RBCs, leading to reduced ability of the RBCs to withstand **oxidative stress** (see Figure 4-8). The stress leads to oxidation of sulfhydryl groups on hemoglobin, which then precipitate as **Heinz bodies**.

This disorder is **X-linked**, and variants are common in the **black and Middle Eastern/Mediterranean populations**. It is associated with resistance to malarial infection. Women may have both normal and abnormal cells if they are heterozygous. Episodes are **self-limited**, as erythropoiesis leads to the production of reticulocytes with normal enzyme activity. Hemolysis is both **intravascular and extravascular**.

PRESENTATION

Often asymptomatic. History of neonatal jaundice and cholelithiasis. Episodic fatigue, pallor, and other symptoms of anemia may result. Exam may reveal jaundice and splenomegaly. Hemolysis often results from exposure to oxidative stress such as:

- **Drugs:** Sulfonamides, primaquine, chloroquine, and nitrofurantoins, among others.
- **Infections:** Viral hepatitis, typhoid fever, pneumonia.
- **Other:** Fava beans.

DIAGNOSIS

Measure **G6PD enzyme activity** (will be normal at time of hemolysis due to presence of young cells, but will be decreased when no hemolysis is present),

KEY FACT

In glucose-6-phosphate dehydrogenase (G6PD) deficiency, RBCs cannot withstand oxidative stress, especially from drugs and infection, leading to hemolysis.

FLASH BACK

G6PD reduces nicotinamide adenine dinucleotide phosphate to reduced nicotinamide adenine dinucleotide phosphate, which reduces glutathione (GSSG) to reduced glutathione (GSH) which then protects against oxidants like hydrogen peroxide (H_2O_2).

FLASH FORWARD

In G6PD-deficient patients, avoid sulfonamides, primaquine, chloroquine, and fava beans.

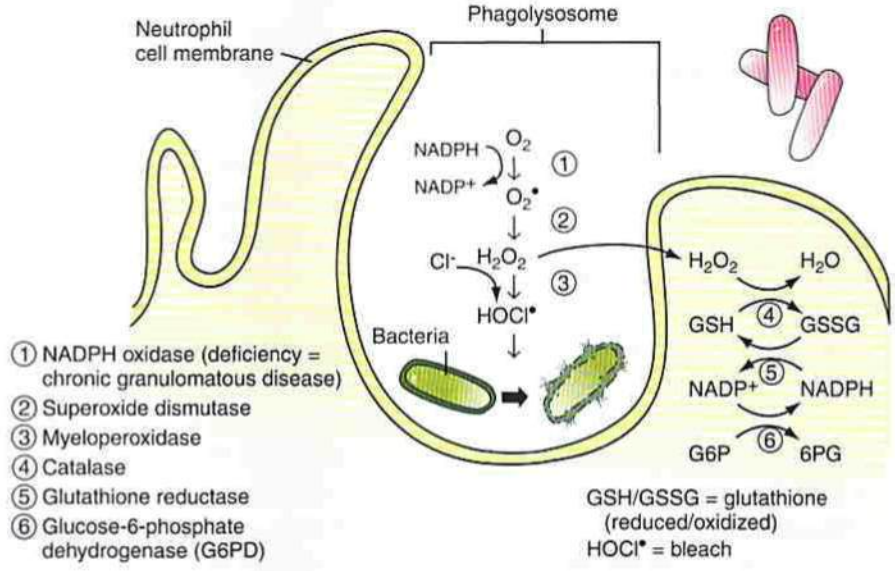


FIGURE 4-8. Red blood cells and oxidative stress. G6P = glucose-6-phosphate; NADP = nicotinamide adenine dinucleotide phosphate; NADPH = reduced nicotinamide adenine dinucleotide phosphate; 6PG = 6-phosphogluconate.

indirect bilirubin (increased), and **serum haptoglobin** (decreased). CBC with reticulocyte count will reveal **hemoglobinemia** and **decreased hematocrit**. Urinalysis shows hemoglobinuria. PBS shows **Heinz bodies** and **bite cells** (result from splenic removal of Heinz bodies). Abdominal ultrasound may reveal splenomegaly and gallstones. Differential diagnosis includes other anemias (especially hemolytic).

TREATMENT

- Avoid precipitating factors.
- Provide O_2 and rest during episodes.
- Exchange transfusions if severe.
- Light therapy in infants.

PROGNOSIS

Patients can remain healthy if they avoid precipitating factors, but complications include neonatal jaundice that may lead to kernicterus, a type of brain damage caused by pathologically high levels of bilirubin.

FLASH FORWARD

Hereditary spherocytosis (HS) results from a defect in the proteins involved in vertical interactions (ankyrin, spectrin, band 3, and protein 4.2), while hereditary elliptocytosis results from a defect in the proteins involved in horizontal interactions (spectrin, protein 4.1, and glycophorin). Both groups of proteins work to maintain membrane integrity.

Pyruvate Kinase Deficiency

Autosomal recessive enzyme dysfunction leading to anemia that is **chronic** rather than episodic.

Hereditary Spherocytosis

Deficiency of spectrin, ankyrin, or other cytoskeletal protein leads to RBC fragility. The cells are forced into a **spherical shape** because of a **loss of membrane fragments**. Spherical cells are less deformable, become trapped within the spleen, and are then phagocytosed.

Presentation

Stable course of **anemia, splenomegaly, and jaundice**. Some are asymptomatic. Some may have **cholelithiasis** as well. Family history especially in an **autosomal dominant** pattern.

Diagnosis

Perform **osmotic fragility test**, which will show lysis of RBCs in hypotonic salt. **Increased mean corpuscular hemoglobin concentration (MCHC)** is seen due to cell dehydration. CBC will reveal minimal anemia with reticulocytosis, and a PBS will show **spherocytes**. Increased levels of **indirect bilirubin** may be detected. Differential includes anemia, biliary disease, hyperbilirubinemia, and autoimmune hemolytic anemia (which may also have spherocytes).

Treatment

- Splenectomy.
- Transfusion if severe.
- Phototherapy in infants.
- Supplemental folic acid and iron.

Prognosis

Possible complications include aplastic crisis triggered by parvovirus infection, infections after splenectomy, cholelithiasis, and hemochromatosis from multiple transfusions.

FLASH BACK

Hemoglobin has two forms: T (taut) has a low affinity for O_2, and R (relaxed) has a high affinity.

FLASH BACK

O_2 binding is cooperative and is **decreased** by Cl^-, H^+, CO_2, 2-3-diphosphoglycerate (2,3-DPG), and high temperatures.

FLASH BACK

Fetal hemoglobin has lower affinity for 2,3-DPG than adult hemoglobin and, as a result, has higher affinity for O_2.

Sickle Cell Disease

Point mutation (substitution of **valine** for glutamic acid at position 6) in the **β-globin chain gene** leads to production of abnormal hemoglobin, **HbS**. Common in the **African** and **African-American** populations.

Adults normally have a large amount of HbA and small amounts of HbA_2 and HbF (fetal hemoglobin). However, those with sickle cell have at least one allele for HbS. Many variants of sickle cell exist including:

Sickle cell trait: Heterozygotes with an HbA and an HbS allele (HbSA); results in resistance against malarial infection.
Sickle cell disease: Homozygotes have two HbS alleles (HbSS).
Other: Heterozygotes with an HbS and an HbC allele (HbSC).
Order of severity: HbSS > HbSC > HbSA.

HbS undergoes aggregation and polymerization when **deoxygenated**, leading to **sickle-shaped** cells which are subject to **splenic destruction** (seen in Figure 4-9). These cells make the blood **hyperviscous**, which can lead to **microvascular occlusion**. Sickling may occur as a result of **hypoxia or a fall in pH**, which reduces the O_2 affinity of hemoglobin. This is worsened by **dehydration**, which increases MCHC and aggregation of HbS molecules. The presence of HbF prevents polymerization of HbS.

Presentation

Because HbF prevents polymerization of HbS, disease may not present until newborns are 6 months old.

- Pallor from chronic hemolytic anemia.
- Vaso-occulsion causes swelling of hands and feet (**hand-foot syndrome**) and pulmonary infiltrate (**acute chest syndrome**).



FIGURE 4-9. Sickle cell peripheral blood smear. Note the sickle cells as well as anisocytosis, poikilocytosis, and nucleated red blood cells.

- **Painful vaso-occlusive crisis** in joints, abdomen, viscera, lungs, liver, and penis.
- Increased susceptibility to encapsulated bacteria such as **pneumococcus** and ***Haemophilus influenzae***, as well as to ***Salmonella*** **osteomyelitis**.
- Infarctions of lungs and spleen occur, and **autosplenectomy** (see Figure 4-10) is complete by age 6 years.
- **Aplastic crises** brought on by **parvovirus** infection.
- Adults may develop chronic leg ulcers.

Diagnosis

- **Hb electrophoresis** reveals high levels of HbS.
- Mixing blood with a **reducing agent** like metabisulfate will cause sickling; positive in both sickle cell trait and disease.

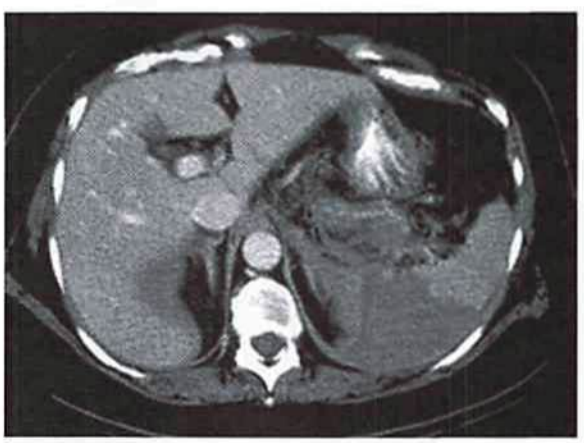


FIGURE 4-10. Splenic infarction. The splenic artery lacks collateral supply, making the spleen particularly susceptible to ischemic damage. Coagulative necrosis has occurred in a wedge shape along the pattern of vascular supply. Individual sickle cells cause generalized splenic infarcts that result in autospelenctomy.

- CBC shows anemia, reticulocytosis, leukocytosis, thrombocytosis.
- Peripheral smear (see Figure 4-9) reveals sickled RBCs, polychromasia, nucleated RBCs, and **Howell-Jolly bodies.**
- Serum bilirubin and fecal/urinary urobilinogen will be elevated; haptoglobin levels will be low.
- Skull X-ray shows **"crew cut"** pattern due to extramedullary hematopoiesis.
- Differential diagnosis includes other anemias, other hemoglobinopathies, and osteomyelitis.

Treatment

- Folic acid supplementation.
- Blood transfusion.
- Penicillin prophylaxis.
- Pneumococcal vaccine.
- Pain control.
- Bone marrow transplantation.
- **Hydroxyurea** (increases concentration of HbF).

Thalassemia

Genetic syndrome resulting from **decreased synthesis of one of the chains in HbA.** Clinical abnormalities are caused both by the low concentration of hemoglobin and by the excess of the other chain. There are two types of thalassemias, β- and α-thalassemias, discussed below.

KEY FACT

Thalassemia is common among African, Indian, Southeast Asian, and Mediterranean populations.

β-Thalassemia

Defective β-globin chain. Also known as Mediterranean or Cooley's anemia. Three forms exist:

- **Minor:** Heterozygote with underproduced β-globin chain.
- **Major:** Homozygote with absent β-globin chain.
- **HbS/β-thalassemia:** Combination of sickle cell and β-thalassemia. Most common form in the United States and in the Mediterranean.

All lead to lack of HbA and **aggregation of α-chains.** Aggregation leads to **decreased RBC life span** and apoptotic death of RBC precursors, resulting in ineffective erythropoiesis. **Fetal hemoglobin is increased** as a compensatory mechanism, but is inadequate.



MNEMONIC

β-ThalaSSemia:

3 S's

Splenomegaly
Hemo**S**iderosis
Skeletal deformities

Presentation

Anemia, splenomegaly from extramedullary hematopoiesis, **hemosiderosis** (from increased iron absorption and repeated transfusion), **skeletal deformities** (including **"crew cut"** appearance of skull on X-rays due to thinning of cortical bone and peripheral new bone formation).

Diagnosis

Microcytic hypochromic RBC morphology on PBS.

Treatment

Blood transfusions.

Prognosis

Complications may include growth retardation, death at an early age, cardiac failure, and other organ damage from hemosiderosis.

α-Thalassemia

- **Decreased production of α-globin** due to mutation in one or more of the four α-globin genes. There is no compensatory increase in any other chains, but there is a relative excess of other chains including β, γ, and δ.
- α-thalassemia is prevalent among **Asian** and **African** populations.

Presentation

Depends on the number of genes mutated or deleted.

- **Silent carrier state:** Only **one** α-globin gene affected; **asymptomatic.**
- **α-thalassemia trait: Two** genes deleted; similar to β-thalassemia minor with **minimal anemia.**
- **Hemoglobin H disease: Three** α-globin genes affected; **HbH** (tetramers of β-globin chains) form; HbH has high O_2 affinity; **anemia disproportionate** to the amount of hemoglobin.
- **Hydrops fetalis:** Deletion of **all four** genes; **Hb Barts** (tetramers of γ-globin chains) has extremely high O_2 affinity; severe anemia; will lead to **intrauterine death** unless intrauterine transfusion is performed; fetus shows edema, pallor, and hepatosplenomegaly.

Diagnosis

Based on **microcytic, hypochromic** blood smear, and clinical presentation.

Paroxysmal Nocturnal Hemoglobinuria

Acquired defect in RBC membrane leads to **intravascular** hemolysis. Mutation is in the glycosylphosphatidylinositol (GPI) protein anchor. Many of the GPI-linked proteins inactivate complement, so without them, cells are subject to lysis by endogenous complement. Platelets and granulocytes can be affected also.

Presentation

Hemoglobinuria on awakening; **hemosiderinuria** can lead to iron deficiency.

Diagnosis

Based on clinical presentation. Flow cytometry can detect abnormalities in red cell membranes.

Prognosis

This can evolve into aplastic anemia and acute leukemia.



Warm weather is **GGG**reat (IgG).
Cold ice cream...**MMM** (IgM).

Immunohemolytic Anemias

Antibodies are produced that lead to destruction of RBCs. Due to the presence of antibodies, these anemias are **Coombs-positive**. There are three types of immunohemolytic anemias: warm antibody, cold agglutinin, and erythroblastosis fetalis as discussed below.

Warm Antibody Hemolytic Anemia

IgG autoantibodies bind RBCs, leading to spheroidal transformation. Spherocytes are sequestered in spleen (**extravascular** hemolysis).

Presentation

Elevated bilirubin (jaundice, pigment gallstones), reticulocytosis, and splenomegaly. Often associated with **SLE, Hodgkin's lymphoma, chronic lym-**

phocytic leukemia (CLL), or certain drugs (**α-methyldopa, penicillin, cephalosporins**).

Diagnosis

Spherocytosis, positive direct Coombs' test (anti-Ig Ab added to patient's RBCs leads to agglutination if RBCs have IgG attached).

Cold Agglutinin Immune Hemolytic Anemia

IgM autoantibodies bind RBCs optimally at 30°C. Some **intravascular hemolysis** is seen, especially in distal body parts. IgM is released when cells warm, leaving **C3b** bound to membrane. Thus, RBCs are also subject to **extravascular hemolysis**.

Presentation

Episodic hyperbilirubinemia. May also have hemoglobinemia and hemoglobinuria.

- **Acute:** Often in recovery phase after infectious **mononucleosis** or **mycoplasmal pneumonia.**
- **Chronic:** Associated with **lymphoproliferative neoplasms**; may be associated with **Raynaud's** phenomenon (see Figure 4-11) due to vascular obstruction.

Erythroblastosis Fetalis

Maternal alloimmunization to **D antigen of Rh blood group** leads to destruction of fetal RBCs. Usually, the mother is D (Rh negative) and the fetus is D (Rh positive). May also occur in setting of **ABO incompatibility**; in these cases, the mother is often O and the fetus is A or B.

KEY FACT

Erythroblastosis fetalis:
Mom = Rh negative
Fetus = Rh positive

Presentation

Fetal hemolytic anemia

Diagnosis

Test maternal and fetal blood for presence of antibodies.

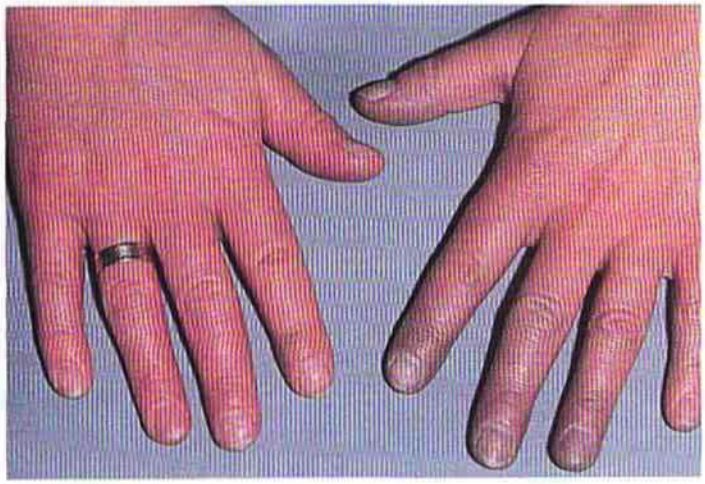


FIGURE 4-11. Raynaud's phenomenon. (Reproduced, with permission, from Wolff K, Johnson RA, Surrmon D, *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed, New York: McGraw-Hill, 2005: 403.)

Prognosis

Stillbirth, **hydrops fetalis** (fetal heart failure), **kernicterus** (unconjugated bilirubin damages basal ganglia and other CNS structures, leading to neurologic damage).

Microangiopathic Anemia

Mechanical trauma caused by narrowed vessels leads to **intravascular** hemolysis seen in disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), SLE, or malignant hypertension.

MNEMONIC

Microangiopathic anemia can be caused by THUDS:

TTP
Hypertension (malignant)
HUS
DIC
SLE

Presentation

Related to clinical syndrome causing hemolysis. Hemolysis is usually clinically irrelevant except in TTP and HUS.

Diagnosis

Schistocytes (helmet cells) on PBS.

Cardiac Traumatic Hemolytic Anemia

Shear stress due to the turbulent blood flow and abnormal pressures that occur with **prosthetic valves** leads to RBC damage.

Anemia of Decreased Red Blood Cell Production

Megaloblastic Anemia

Deficiency in vitamin B_{12} or folate (coenzymes in DNA synthesis) leads to **delayed DNA replication,** although cytoplasmic maturation is normal.

- **Vitamin B_{12} deficiency** can be caused by:
  - Decreased intake (especially in **vegans**).
  - Impaired absorption (**pernicious anemia**, gastrectomy, malabsorption, **ileal resection**, ***Diphyllobothrium latum*/fish tapeworm** infection, **blind loop syndrome**, broad-spectrum antibiotics).
  - Increased requirement (**pregnancy**, hyperthyroidism).
- **Folic acid deficiency** can be caused by:
  - Decreased intake (**alcoholics**).
  - Impaired absorption (sprue, phenytoin, oral contraceptives).
  - Increased loss (hemodialysis).
  - Increased requirement (**pregnancy**, infancy, increased hematopoiesis).
  - Folic acid antagonist chemotherapy.

FLASH BACK

Subacute combined degeneration of the spinal cord: Vitamin B_{12} deficiency leads to demyelination of the dorsal and lateral columns of the spinal cord. As a result, patients exhibit ataxia, hyperreflexia, and decreased position and vibration sensation.

Presentation

Anemia; **subacute combined degeneration** of the spinal cord in vitamin B_{12} deficiency.

Diagnosis

PBS may show **pancytopenia, oval macrocytosis,** and **hypersegmented neutrophils** (> 5 lobes); bone marrow shows **megaloblastic hyperplasia.** Vitamin B_{12} and folate levels can be measured.

KEY FACT

Use Schilling's test to check if vitamin B_{12} deficiency is related to a lack of intrinsic factor.

- In pernicious anemia, **anti-intrinsic factor antibodies** are present and **Schilling's test** shows that the absorption of vitamin B_{12} improves by administration of intrinsic factor.

Treatment

Requires vitamin B_{12} and/or folate supplementation.

Iron Deficiency Anemia

Iron is necessary for the **production of heme**; therefore iron deficiency decreases the O_2-carrying capacity of RBCs. Deficiency can be caused by:

- Increased requirement: **Pregnancy**, infants, and preadolescents.
- Dietary deficiency: Exclusively breast-fed infants after 6 months of age, elderly.
- Chronic blood loss: **Menorrhagia, gastrointestinal bleeding.**

Presentation

Pallor, fatigue, angina pectoris in persons with CAD, gastritis, glossitis, koilonychias (spooning of nails), can be associated with **Plummer-Vinson syndrome** (upper esophageal web).

Diagnosis

Decreased hemoglobin and hematocrit. Peripheral smear shows **microcytic, hypochromic** RBCs. Laboratory studies reveal **decreased serum iron, increased total iron-binding capacity** (TIBC), and **decreased ferritin**.

KEY FACT

Lab findings in iron deficiency anemia:
↓ TIBC
↓ serum iron, ferritin

Treatment

Relieved by iron supplementation.

Anemia of Chronic Disease

Chronic inflammatory or neoplastic disease **reduces production of erythropoietin** as a result of cytokine release. Usually characterized by marrow hypoproliferation and impaired iron reutilization. Typical causes include:

- **Chronic infections:** Osteomyelitis and bacterial endocarditis, among others.
- Chronic immune disorders: **Rheumatoid arthritis.**
- **Renal disease.**
- **Neoplasms:** Hodgkin's disease and lung carcinoma, among others.

Presentation

Symptoms of the chronic disease along with mild anemia (fatigue, pallor).

Diagnosis

Decreased hemoglobin and hematocrit; peripheral smear may show microcytic, hypochromic RBCs or normocytic, normochromic RBCs; **decreased serum iron, decreased TIBC, increased ferritin**, and **abundant iron stored** in marrow macrophages.

KEY FACT

Lab findings in anemia of chronic disease:
↓ TIBC.
↓ serum iron.
↑ serum ferritin, iron stored in macrophages.

Treatment

Anemia may be resolved by administering erythropoietin and treating the underlying condition.

Prognosis

Overall prognosis depends on the underlying condition.

Aplastic Anemia

Pancytopenia characterized by severe **anemia**, **neutropenia**, and **thrombocytopenia**. Failure or destruction of multipotent myeloid stem cells leads to inadequate production or release of differentiated cell lines. Common causes:

- Idiopathic (immune-mediated).
- Radiation.
- Chemicals: Benzene.
- Drugs: Chloramphenicol, sulfonamides, alkylating agents, antimalarial drugs, antimetabolites.
- Viral agents (parvovirus B19, EBV, HIV, HCV).
- Fanconi's anemia.

FLASH BACK

Aplastic anemia is a common adverse effect of chloramphenicol; it may or may not reverse with discontinuation of the drug.

Presentation

Onset usually gradual:

Anemia → fatigue, malaise, pallor.
Thrombocytopenia → purpura, mucosal bleeding, petechiae.
Neutropenia → infection.

Diagnosis

- **CBC:** Decreased RBC, WBC, and platelet count.
- **Marrow biopsy: Hypocellular bone marrow** (see Figure 4-12), decreased erythrocytic and granulocytic precursors, decreased megakaryocytes, and **fatty infiltration.**
- **Peripheral smear: Pancytopenia**, normochromic, normocytic, no reticulocytosis, and no splenomegaly.

Treatment

- Withdrawal of offending agent.
- Immune therapy: Antithymocyte globulin, cyclosporine.
- Allogenic bone marrow transplantation.
- RBC and platelet transfusion.
- G-CSF, GM-CSF.

Prognosis

- If adverse effect of drug, withdrawal may lead to recovery.
- If idiopathic, poor prognosis.

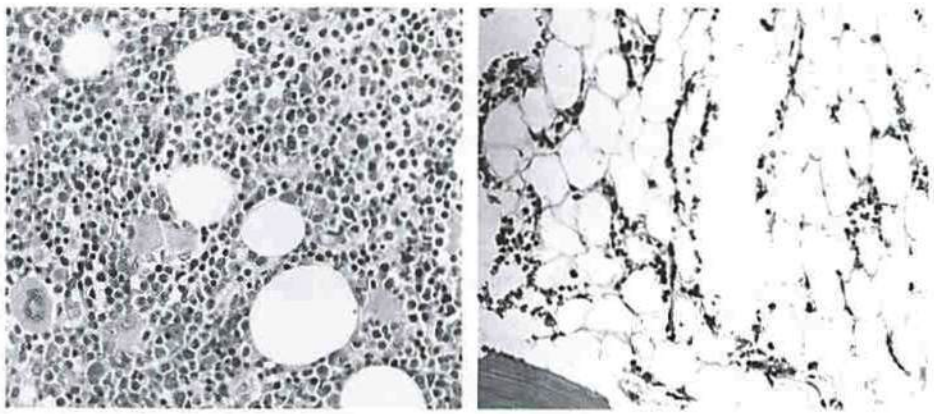


FIGURE 4-12. Bone marrow biopsy of aplastic anemia. Note hypocellular bone marrow, decrease in erythrocytic and granulocytic precursors and megakaryocytes, and fatty infiltration. (Reproduced, with permission from Lichtman MA, Beutler E, Kipps TJ, et al., *Williams Hematology*, 7th ed, New York: McGraw-Hill, 2006: 425.)

Pure Red Cell Aplasia

Rare form of marrow failure affecting erythropoiesis but not granulopoiesis or thrombopoiesis. Causes include:

- **Primary** (possible autoimmune mechanism).
- **Secondary** to neoplasm (**thymoma**, leukemia of large granular lymphocytes).

Presentation

Fatigue, pallor, malaise.

Diagnosis

CBC and peripheral smear show decreased RBCs. Marrow biopsy shows decreased erythroid precursors. Reticulocyte count often < 0.1%.

Treatment

Resection, immunosuppressive therapy, and/or plasmapheresis.

Prognosis

If secondary to thymoma, resection of neoplasm may lead to resolution; other treatments may lead to improvement.

Myelophthisic Anemia (Leukoerythroblastosis)

Destruction of bone marrow or disturbance of marrow architecture because of **space-occupying lesion** leads to decreased production of RBCs and other blood elements. Often accompanied by **reactive fibrosis** which can lead to release of precursor cells into blood. Caused by:

- **Metastatic cancer:** From breast, lung, prostate, thyroid, or adrenals.
- Multiple myeloma.
- Leukemia.
- Osteosclerosis.
- Lymphoma.
- Myelofibrosis.

Presentation

Fatigue, malaise, pallor, infection, mucosal bleeding, petechiae (see Figure 4-13), purpura; symptoms of underlying cause.



FIGURE 4-13. Petechiae. (Reproduced, with permission, from Lichtman MA, Beutler E, Kipps TJ, et al., *Williams Hematology*, 7th ed, New York: McGraw-Hill, 2006: Figure XXV-32.)

Diagnosis

Peripheral smear shows **leukoerythroblastosis** (immature red and white cells); bone marrow biopsy shows **tumor cell infiltration**, compressed marrow elements, and possible reactive fibrosis.

Prognosis

Depends on prognosis of underlying cause.

POLYCYTHEMIA/ERYTHROCYTOSIS

Increased concentration of RBCs can be:

- **Relative:** Due to decreased plasma volume (volume contraction). Caused by **H_2O deprivation**, prolonged vomiting, diarrhea, or diuretics.
- **Absolute:** Increased total red cell mass:
  - Primary:
    - Intrinsic abnormality of myeloid stem cells: **Polycythemia vera.**
    - **Congenital:** Mutation of erythropoietin receptor leads to increased sensitivity.
  - Secondary:
    - Increased levels of erythropoietin.
      - Physiologic: Lung disease, high altitude, cyanotic heart disease.
      - Erythropoietin-secreting tumors: Renal cell carcinoma, hepatocellular carcinoma, cerebellar hemangioblastoma.

KEY FACT

Relative polycythemia is caused by **decreased** plasma volume. Absolute polycythemia is caused by **increased** total red cell mass.

Presentation

Varies depending on cause; may include:

- **Cyanosis** due to stagnation of blood in peripheral vessels.
- **Thrombotic phenomena**: DVT, MI, stroke, Budd-Chiari syndrome, and bowel infarction.
- **Bleeding phenomena**: Hemorrhagic strokes, epistaxis, bleeding gums; hypertension, headache, dizziness, and GI symptoms.

Diagnosis

Increased hematocrit and increased red cell volume in absolute erythrocytosis; bone marrow biopsy if polycythemia vera.

Prognosis

Varies based on cause.

HEMORRHAGIC DISORDERS

Result from a variety of conditions. Some can be caused by abnormalities of vessels and platelets, some by imbalances in clotting factors, and others by both (see Table 4-4).

Vessel Wall Abnormalities

Disruption of the vessel wall leads to hemorrhage. Causes include:

- **Scurvy:** Vitamin C deficiency results in collagen abnormality and decreased wall strength. Gingival hemorrhages, bleeding into muscles and subcutaneous tissue, and cutaneous petechiae around hair follicles are common.

TABLE 4-4. Causes of Hemorrhagic Disorders

PRIMARY (RELATED TO VESSELS AND/OR PLATELETS)	SECONDARY (RELATED TO CLOTTING FACTORS)	COMBINED (RELATED TO PLATELETS AND CLOTTING FACTORS)
Vessel wall abnormalities	Hemophilia A	Von Willebrand's disease
Platelet disorders	Hemophilia B	DIC
Thrombocytopenia	Vitamin K deficiency	Liver disease
Idiopathic thrombocytopenic purpura		Dilutional
Drug-induced		
HIV-associated		
Thrombotic microangiopathies		
Platelet function abnormalities		
Von Willebrand's disease		
Bernard-Soulier disease		
Aspirin		
Glanzmann's thrombasthenia		

- **Ehlers-Danlos syndrome:** Inherited collagen and/or elastin abnormality leads to decreased vessel wall strength, hyperelasticity of skin, hypermobility of joints, and tissue fragility.
- **Cushing's syndrome:** Protein wasting leads to loss of perivascular support.
- **Aging:** Atrophy of collagen leads to decreased wall strength.
- **Henoch-Schönlein purpura:** Hypersensitivity vasculitis (often associated with upper respiratory infection) results in immune complex deposition on vessel walls. Symptoms include palpable purpura, polyarthralgias, fever, painful focal GI hemorrhages, and acute glomerulonephritis.
- **Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome):** Autosomal dominant mutation leads to dilated, tortuous blood vessels with thin walls in skin and mucous membranes.
- **Waldenström's macroglobulinemia:** Hyperviscous blood damages vessels.
- **Amyloidosis:** Deposition of amyloid in vessel walls.
- **Infections:** Meningococcemia, septicemia, infective endocarditis, rickettsiosis, and others lead to vasculitis and/or DIC.

PRESENTATION

Usually mild (petechiae, purpura in skin, or mucous membranes); occasionally more severe (hemorrhages into joints and muscles, menorrhagia, epistaxis, GI bleeding, hematuria).

DIAGNOSIS

Platelet count, prothrombin time (PT), and partial thromboplastin time (PTT) are usually normal. Bleeding time is occasionally prolonged.

Note: Platelet function analyzer (PFA)-100 test has replaced bleeding time in many institutions.

PROGNOSIS

Depends on specific cause.

FLASH FORWARD

Heparin-induced thrombocytopenia (HIT):

- Type I occurs rapidly and is clinically insignificant, resulting from platelet aggregation.
- Type II develops after 5–14 days; life-threatening thrombosis; immune reaction against complex of heparin and platelet factor IV. Can occur earlier if previously exposed to heparin.

Thrombocytopenia

Reduction in number of platelets leads to decreased ability to form clots. Results from decreased production, decreased survival, sequestration, and dilution of platelets. Specific causes include:

- Bone marrow diseases such **aplastic anemia** and **acute leukemia.**
- Drugs: Alcohol, quinidine, **heparin**, sulfa, **cytotoxic drugs**, and thiazide diuretics.
- Infections such as measles, **HIV**, infectious mononucleosis, CMV, *Haemophilus influenzae* type B.
- **Hypersplenism** leads to sequestration of platelets.
- **Transfusions** result in dilution of platelets and clotting factors; may additionally lead to destruction of platelets.
- **Systemic lupus erythematosus.**
- **Disseminated intravascular coagulation:** Activation of coagulation cascade leads to **microthrombi** and consumption of platelets and coagulation factors **(especially II, V, VIII, and fibrinogen)**; characterized by both thrombosis and hemorrhage; results from the release of tissue thromboplastin or activation of the intrinsic pathway.
  - Common causes: **Obstetric** complications (toxemia, amniotic fluid emboli, retained fetus, or abruptio placentae), **gram-negative sepsis**, transfusion, trauma, **malignancy** (especially of the lung, pancreas, prostate, and stomach), acute pancreatitis, nephrotic syndrome.
  - Diagnosis: **Increased PT, PTT, fibrin, fibrin split products (D-dimers), thrombin time, and bleeding time; decreased platelet count.** Helmet-shaped cells and schistocytes seen on blood smear occasionally.
  - Prognosis: Can lead to organ damage and shock; poor prognosis.
  - Treatment: Treat underlying cause and give supportive therapy.
- **Idiopathic thrombocytopenic purpura:** Thrombocytopenia with normal or increased megakaryocytes. **Antiplatelet antibodies** attach to platelets and lead to removal by splenic macrophages. No splenomegaly.
  - **Children: Acute**, self-limited reaction to viral infection or immunization; treat only if severe.
  - **Adults: Chronic**, autoimmune condition; occurs more often in **females**; treat with steroids and/or splenectomy.
- **Thrombotic microangiopathies:** Result from **hyaline microthrombi** (platelet aggregates surrounded by fibrin) leading to **thrombocytopenia** and microangiopathic anemia (PBS shows **schistocytes** and **helmet cells**).
  - **Thrombotic thrombocytopenic purpura:** Usually in **adult** females; also includes fever, **transient neurologic deficits**, and renal failure; increased LDH.
  - **HUS:** Usually in **children** following ***Escherichia coli*** O157:H7 infection; dominance of **acute renal failure** rather than neurologic deficits.

KEY FACT

DIC laboratory findings:
↑ PT, PTT, fibrin, fibrin split products, thrombin time, and bleeding time.
↓ platelet count.

Presentation

Characterized by bleeding from small vessels which leads to **petechial, purpural, mucosal, and intracranial hemorrhage**. Platelet count below 100,000/mm^3 is considered pathologic, though spontaneous bleeding does not typically occur until the platelet count falls below 20,000/mm^3.

KEY FACT

Laboratory findings in thrombocytopenia:
↓ **platelet count**
↑ **bleeding time**
No change in PT and PTT.

Diagnosis

- **Decreased platelet count** is the main diagnostic finding.
- **Prolonged bleeding time** occasionally seen; often will be normal and rarely used in diagnosis.
- Bone marrow aspiration: Megakaryocytes increased if decreased platelet production, decreased if increased platelet destruction; usually not performed.

Prognosis

Varies with underlying cause.

Platelet Function Abnormalities

Qualitative platelet dysfunction that takes place in the setting of normal platelet counts. Caused by:

- Defects in platelet adhesion:
  - **von Willebrand's disease:** Most common hereditary bleeding disorder; **autosomal dominant** deficiency of von Willebrand's factor (vWF) which normally carries **factor VIII** and mediates adhesion of platelets to endothelium in vascular injury; disease is characterized by:
    - Impaired adhesion → prolonged bleeding time.
    - Mild quantitative deficiency of factor VIII → prolonged aPTT.
  - **Bernard-Soulier disease: Autosomal recessive** disorder in which platelets are abnormally large and lack platelet-surface **glycoprotein Ib** which is needed for platelet adhesion.
- Defects in platelet aggregation:
  - **Aspirin:** Acetylates and inactivates cyclooxygenase (COX), an enzyme necessary for the production of **thromboxane A2**, a platelet aggregant.
  - **Glanzmann's thrombasthenia:** Hereditary deficiency of platelet-surface **glycoproteins IIb and IIIa**, which are required for forming fibrinogen bridges between platelets.

Presentation

Mucocutaneous bleeding.

Diagnosis

Laboratory tests (PT, PTT, bleeding time, platelet count).

Prognosis

Depends on underlying cause.

Clotting Factor Deficiencies

Lack of clotting factors leads to bleeding, especially from larger vessels. These deficiencies are described below.

Hemophilia

X-linked deficiency of factor VIII; also known as classic hemophilia.

Hemophilia B

X-linked deficiency of factor IX; also known as Christmas disease.

Vitamin K Deficiency

Leads to deficiency of **factors II, VII, IX, X,** and **proteins C and S.** In adults, caused by fat malabsorption due to pancreatic or small-bowel disease. In infants, caused by deficient exogenous vitamin K (not present in breast milk) and incomplete intestinal colonization by bacteria that synthesize vitamin K.

Liver Disease

Hepatocellular damage prevents the production of **all coagulation factors except vWF,** as they are exclusively formed in the liver. Liver disease may lead to **hypersplenism** and **overt thrombocytopenia.** As a result, PT, PTT, thrombin time, and bleeding time are prolonged.

FLASH BACK

Clotting cascade physiology: vWF carries factor VIII and mediates platelet adhesion to the endothelium.

KEY FACT

Von Willebrand's disease:
↑ bleeding time
↑ aPTT

FLASH FORWARD

Aspirin: Inhibition of COX-1 and COX-2 prevents the conversion of arachidonic acid to various prostaglandins. It is therefore used to treat fever, inflammation, and prevent consequences of clot formation.

FLASH BACK

Partial thromboplastin time: Assesses intrinsic and common pathways; prolongation due to deficiency of **factors V, VIII, IX, X, XI, XII, prothrombin (II), and fibrinogen (I).**

FLASH BACK

Prothrombin time: Assesses extrinsic and common pathways; prolonged due to deficiency of **factor V, VII, X, prothrombin (II), or fibrinogen (I).**

TABLE 4-5. Laboratory Findings in Bleeding Disorders

	Platelet Count	Bleeding Time (PFA-100 test)	PT	PTT	Thrombin Time/Fibrinogen
Vessel abnormalities	–	↑	–	–	–
Thrombocytopenia	↓	↑	–	–	–
Qualitative platelet defects	–	↑	–	–	–
Hemophilia A and B	–	–	↑	–	–
Vitamin K deficiency	–	–	↑	↑	–
Von Willebrand's disease	–	↑	↑	–	–
DIC	↓	↑	↑	↑	↑
Liver disease	↓	↑	↑	↑	↑
Multiple transfusions	↓	↑	↑	↑	↑

Presentation

Macrohemorrhage leads to **hemarthroses** (bleeding into joints), **easy bruising**, and large hematomas rather than petechiae.

Diagnosis

For hemophilia, family history. Laboratory test results for PT, aPTT, and thrombin time (see Table 4-5).

Treatment

Vitamin K or fresh frozen plasma.

Prognosis

Depends on severity and type of condition.

WHITE CELL DISORDERS

Leukopenia

Decreased white blood cell count. Can reflect **neutropenia/granulocytopenia** (decreased number of neutrophils) and/or **lymphopenia** (decreased number of lymphocytes).

Neutropenia can result from:

- Decreased production:
  - Aplastic anemia.
  - Certain adverse drug reactions.
  - Inherited conditions.
- Increased destruction:
  - Immunologic disorders.
  - Certain adverse drug reactions.
  - Splenic sequestration.
  - Reduction in numbers due to overwhelming infection.

Lymphopenia may result from:

- HIV.
- Steroids.
- Cytotoxic drugs.
- Viral infections.
- Malnutrition.

Presentation

- **Neutropenia:** Bacterial or fungal infections; malaise, chills, and fever; other signs of specific infections.
- **Lymphopenia:** Viral infections.

Diagnosis

CBC with WBC count and differential.

Prognosis

Depends on degree of reduction in number of cells and cause.

KEY FACT

Drugs that can cause neutropenia or agranulocytosis:

- Chloramphenicol
- Sulfonamides
- Chlorpromazine
- Carbamazepine
- Clozapine
- Colchicine
- Alkylating agents
- Antimetabolites

Reactive Proliferation

Leukocytosis

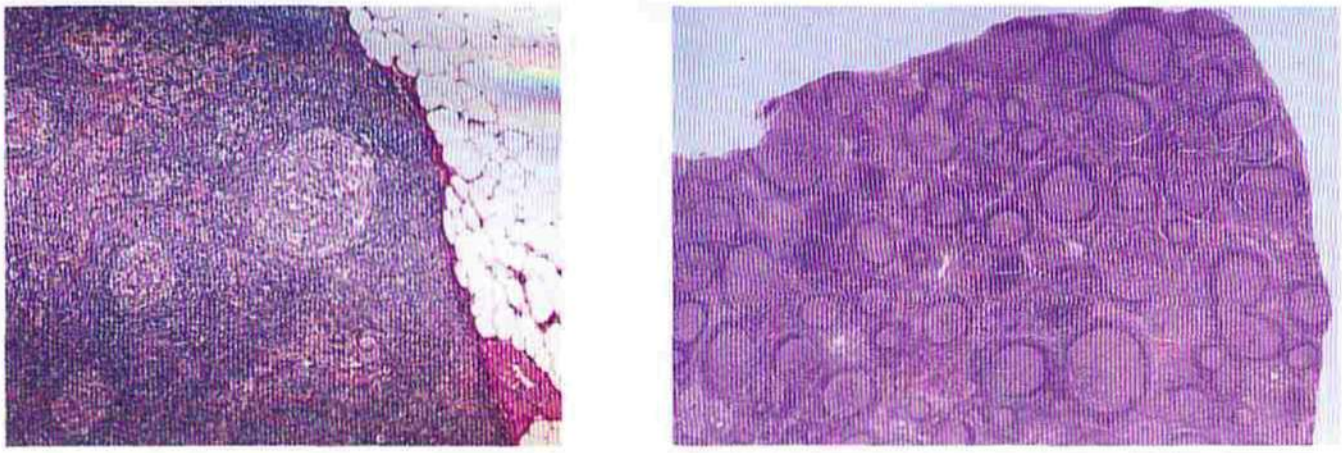
Increased number of white blood cells, usually due to infection or inflammation.

- **Neutrophilic** → Bacterial infection.
- **Eosinophilic** → Allergies, parasitic infections, drugs.

Lymphadenitis

Increased number of white blood cells in lymph nodes (see Figure 4-14), usually due to infection or inflammation; for example:

- **Infectious mononucleosis: EBV**, especially in young adults, infects B lymphocytes and leads to generalized lymphadenopathy. It is characterized by **atypical lymphocytes**, anti-EBV antibodies, and **heterophile antibodies**. It can be associated with sore throat, fever, and hepatosplenomegaly, and is usually self-limited.



A B

FIGURE 4-14. Normal (A) and reactive (B) lymph nodes. (Reproduced, with permission, from Lichtman MA, Beutler E, Kipps TJ, et al., *Williams Hematology*, 7th ed, New York: McGraw-Hill, 2006: Plates XXII-1 and XXII-3.)

Neoplastic Proliferation

Neoplastic proliferation of white blood cells can be classified in many different ways.

Lymphomas are proliferations that form a mass, often located in the lymph nodes. These can be divided into **Hodgkin's lymphomas** with characteristic Reed–Sternberg cells, and **non-Hodgkin's lymphomas (NHLs)**. NHLs can be classified by clinical behavior (low-, intermediate-, or high-grade), by nodular versus diffuse (follicular lymphoma is the only nodular type), by cytology of small vs large cells, and by cell of origin.

KEY FACT

Lymphoma = Proliferation in the form of a mass, often in the lymph nodes; divided into Hodgkin's and non-Hodgkin's.

Leukemias involve the malignant spread of granulocytic or lymphocytic precursors in the bone marrow and the circulation. Cells also frequently infiltrate liver, spleen, and lymph nodes. They can be separated into acute and chronic leukemias (see Figure 4-15). **Acute** forms involve blasts (immature cells), affect children or the elderly, and have a short and drastic course. **Chronic** forms usually have more mature cells proliferating, affect people in mid-life, and have a longer and less devastating course. Leukemias can also be classified by whether they involve **lymphocytic** or **myelogenous** cell types. Often, marrow failure can cause anemia, infections, and hemorrhage by reducing the numbers of RBCs, WBCs, and platelets.

KEY FACT

Leukemia = Proliferation in the bone marrow and bloodstream; divided into acute versus chronic and by myelogenous versus lymphocytic.

Hodgkin's Lymphoma

Malignant proliferation of white blood cells featuring characteristic **Reed–Sternberg cells** (bi- or multinucleated giant cells with eosinophilic nucleoli or "owl eyes"; of CD30+ and CD15+ B-cell origin) in addition to reactive

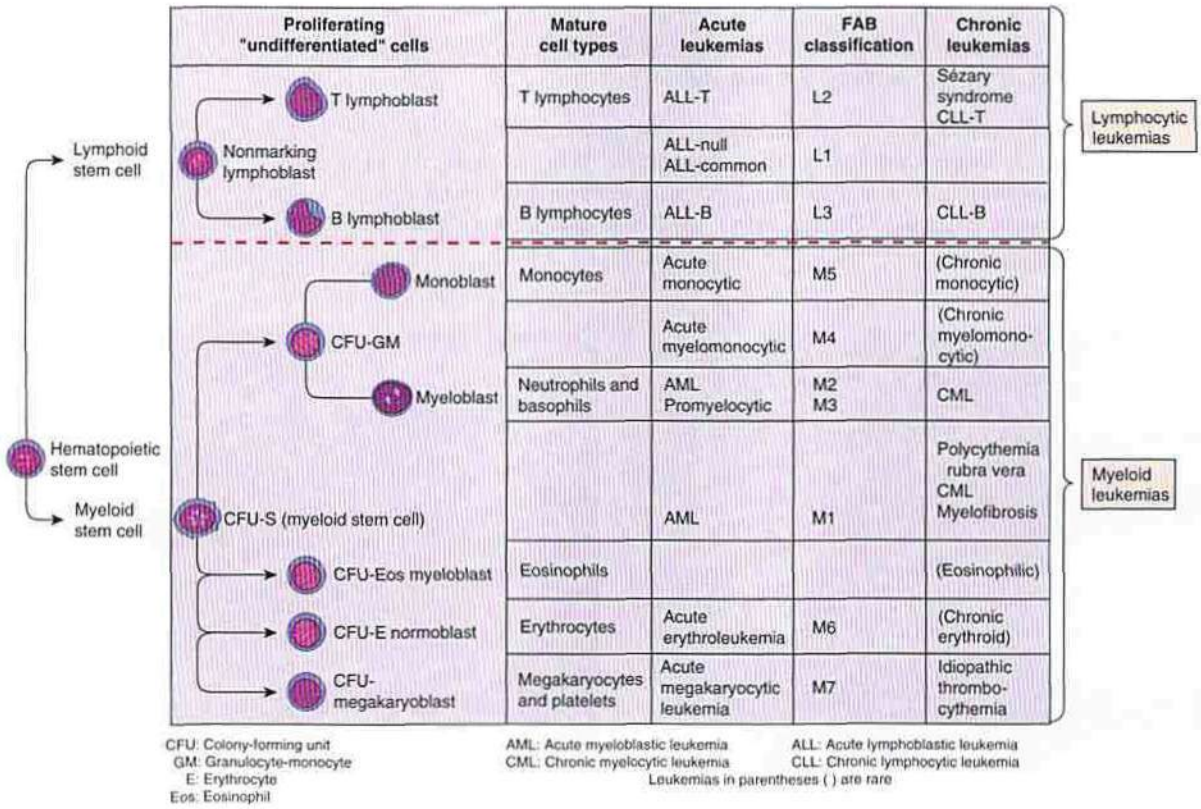


FIGURE 4-15. Leukemia classification. (Modified, with permission, from Chandrasoma P, Taylor CE, *Concise Pathology*, 3rd ed, Stamford, CT: Appleton & Lange, 1998: 410.)

lymphocytes (see Figure 4-16). The majority of cases can be cured. There are four histologic variants: **nodular sclerosing, mixed cellularity, lymphocyte predominant**, and **lymphocyte depleted** (see Figure 4-17 and Table 4-6).

Presentation

Constitutional ("B") symptoms: Low-grade fever, night sweats, and weight loss often present. Typically presents with painless mediastinal lymphadenopathy. About half of cases are associated with **EBV infection**. Age distribution is bimodal (young and old). All types affect men more than women except for the nodular sclerosing type, which affects women more. Spread is contiguous.

Diagnosis

Based on biopsy.

Treatment

Chemotherapy, radiotherapy.

Prognosis

Staging, the best predictor of prognosis, is based on the number of lymph node regions involved, involvement of extralymphatic sites, and extent of dissemination. Because of the high rate of cure due to chemotherapy and radiotherapy, survivors often develop secondary cancers.

Non-Hodgkin's Lymphoma

Malignant lymphoid proliferations of B cells (and occasionally T cells). Often these cases are associated with HIV and immunosuppression. Cells are often located in multiple groups of nodes, and **extranodal** involvement is common. Spread of malignant cells is **noncontiguous**. Can be classified by clinical behavior (low-, intermediate-, or high-grade), by nodular versus diffuse (follicular lymphoma is the only nodular type), and by cytology of small versus large cells.

Presentation

Lymphadenopathy in multiple groups of peripheral nodes. Constitutional symptoms occur with less frequency than in Hodgkin's lymphomas.

KEY FACT

Hodgkin's	Non-Hodgkin's
Reed-Sternberg cells	No Reed-Sternberg cells
Single groups of axial nodes	Multiple groups of peripheral nodes
Contiguous spread	Noncontiguous spread
Constitutional symptoms	Fewer constitutional symptoms
Bimodal (young and old)	Usually seen in those 20–40 years old

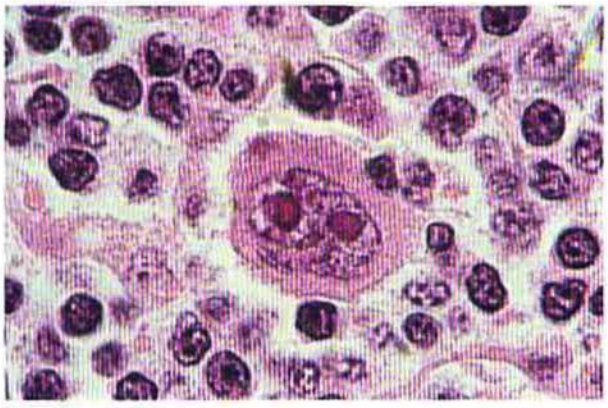
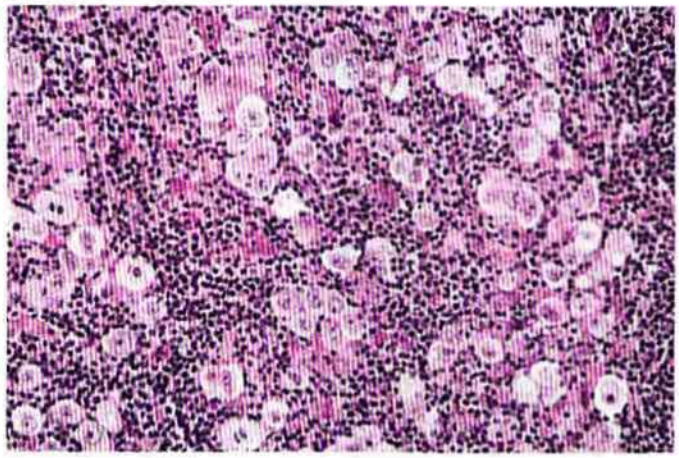
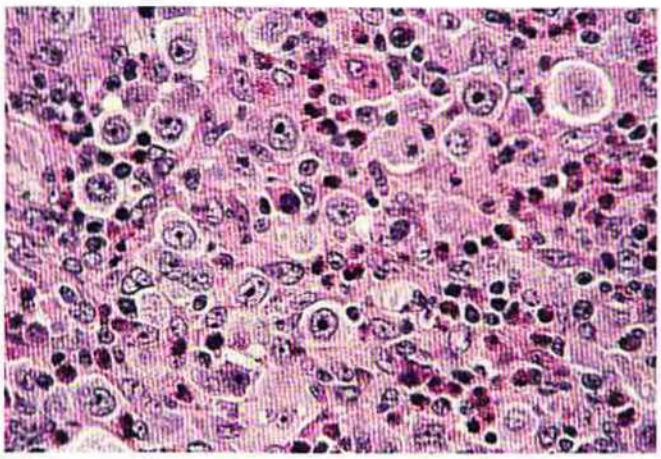


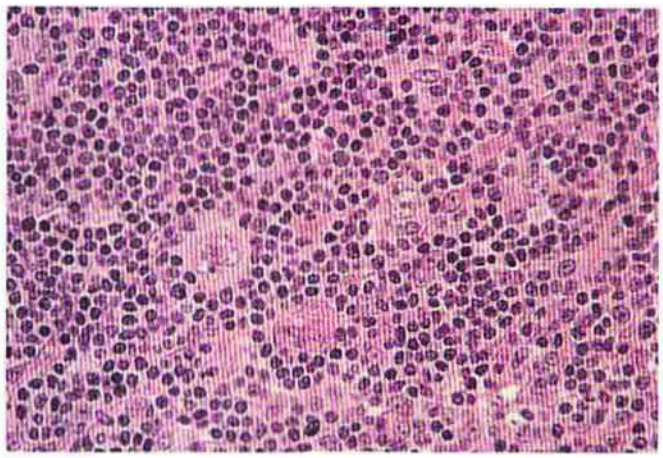
FIGURE 4-16. Reed–Sternberg cells. (Reproduced, with permission, from Lichtman MA, Beutler E, Kipps TJ, et al., *Williams Hematology*, 7th ed, New York: McGraw-Hill, 2006: Plate XXII-32.)



A



B



C

FIGURE 4-17. Histologic types of Hodgkin's lymphoma. (A) Nodular sclerosing; (B) mixed cellularity; (C) lymphocyte predominant. (Reproduced, with permission, from Lichtman MA, Beutler E, Kipps TJ, et al., *Williams Hematology*, 7th ed, New York: McGraw-Hill, 2006: Plates XXII-35, XXII-36, XXII-37.)

Diagnosis

Based on clinical presentation and histologic findings on biopsy (see Table 4-7 and Figure 4-18 for histologic classifications).

Prognosis

Depends on type. While average survival is better in low-grade lymphomas, they are rarely cured. Follicular lymphomas have better survival rates than diffuse forms. Small-cell lymphomas have a better prognosis than large-cell types.

Cutaneous T-Cell Lymphomas

Neoplastic mature T cells proliferate in the dermis and epidermis in **mycosis fungoides** (see Figure 4-19). In a second, leukemic form of the disease known as **Sézary syndrome,** neoplastic cells circulate as well as concentrating in the skin.

KEY FACT

Mycosis fungoides is in the skin. Sézary syndrome is in the blood.

Presentation

Erythematous lesions develop on the skin in the inflammatory premycotic phase, progress along a typical path to the plaque phase, and finally to the tumor phase.

TABLE 4-6. Histologic Types of Hodgkin's Lymphoma and Their Characteristics

Type	Prevalence	No. of Reed-Sternberg Cells	No. of Lymphocytes	Prognosis
Nodular sclerosing ▪ More common in women than men ▪ Cells are grouped into nodules surrounded by **fibrous bands.** ▪ Usually located in cervical, supraclavicular, or mediastinal nodes. ▪ **Lacunar cells** (Reed–Sternberg nucleus surrounded by empty space). ▪ Can be related to EBV infection.	Most common (70%)	+	+++	Excellent
Mixed cellularity ▪ **Typically seen in young males.** ▪ **Also often related to EBV infection.** ▪ **Complete effacement, multiple nodes.** ▪ Eosinophils, plasma cells, histiocytes, and Reed-Sternberg cells with regions of fibrosis	25%	++++	+++	Intermediate
Lymphocyte predominant ▪ Lymphocytes and histiocytes ▪ <35-year-old males ▪ Popcorn cells (Reed-Sternberg cells)	6%	+	++++	Excellent
Lymphocyte depleted ▪ Few lymphocytes with large number of Reed-Sternberg cells and fibrosis ▪ Older males with disseminated disease, HIV patients	Rare	High relative to lymphocytes	+	Poor

Diagnosis

Biopsy reveals CD4+ T cells with characteristic **cerebriform nuclei** proliferating in the dermis. Often there are focal concentrations of neoplastic cells in the epidermis known as **Pautrier's microabscesses**.

Prognosis

Indolent, median survival of 8–9 years; can progress to diffuse large-cell lymphoma.

Acute Lymphoblastic Leukemia

Neoplasm of lymphoblasts (immature B or T cells).

Presentation

Pre–B cell leukemias usually affect children. **Pre-T cell** leukemias often occur with lymphoblastic leukemia; typical clinical picture is an adolescent male with a mediastinal mass. **Onset is sudden,** and patients usually present within days or weeks of symptom onset. **Marrow failure** usually results in fatigue, infection, and bleeding due to anemia, neutropenia, and thrombocytopenia. Bone pain, lymphadenopathy, splenomegaly, hepatomegaly, meningeal spread, and testicular spread are also common with acute lymphoblastic leukemia (ALL). Relapses often in the CNS and testis.

TABLE 4-7. Histologic Types of Non-Hodgkin's Lymphoma and Their Characteristics

Type	Epidemiology	Cell Type	Grade	Genetics	Histology
Small lymphocytic lymphoma ▪ Like a focal mass of **chronic lymphocytic leukemia.** ▪ **Richter's syndrome** or **prolymphocytic transformation** into diffuse B-cell lymphoma occurs in a quarter of cases.	Adults	B	Low		Small, mature looking lymphocytes; lymph nodes are effaced.
Follicular lymphoma (small cleaved cell) ▪ **Most common adult** form; indolent and difficult to cure.	Adults	B	Low	**t(14;18),** translocation of *bcl-2* to Ig heavy chain locus on chromosome 14 leads to overexpression and prevents apoptosis.	Angulated grooved cells typical of those in normal lymphoid follicular center; arranged in nodules.
Diffuse large cell ▪ Often presents with extranodal mass. ▪ Aggressive, but about half are curable.	Adults: 80%; children: 20%	B: 80%; mature T: 20%	Intermediate		
Lymphoblastic lymphoma ▪ **Most common child** form. ▪ Very aggressive; 80% cured, but high relapse rate. ▪ Often presents with **acute lymphocytic leukemia** and **mediastinal mass.**	Children and adults	Immature T	High		**Cell nuclei appear convoluted; arise from thymic lymphocytes.**
Burkitt's lymphoma ▪ Associated with **EBV** ▪ **Very rapidly growing mass.** ▪ Jaw involvement common in endemic African form. ▪ Pelvic/abdominal involvement often occurs in sporadic form.	Children and adults	B	High	t(8;14), *c-myc* overexpressed once moved next to heavy-chain Ig gene on 14.	**Starry-sky** appearance (sheets of lymphocytes with interspersed non-neoplastic macrophages).

Diagnosis

Based on peripheral smear and bone marrow biopsy. Cells have condensed chromatin, **minimal cytoplasm**, and no granules (see Figure 4-20). Surface markers are also assessed to differentiate from acute myeloid leukemia.

Treatment

Chemotherapy.

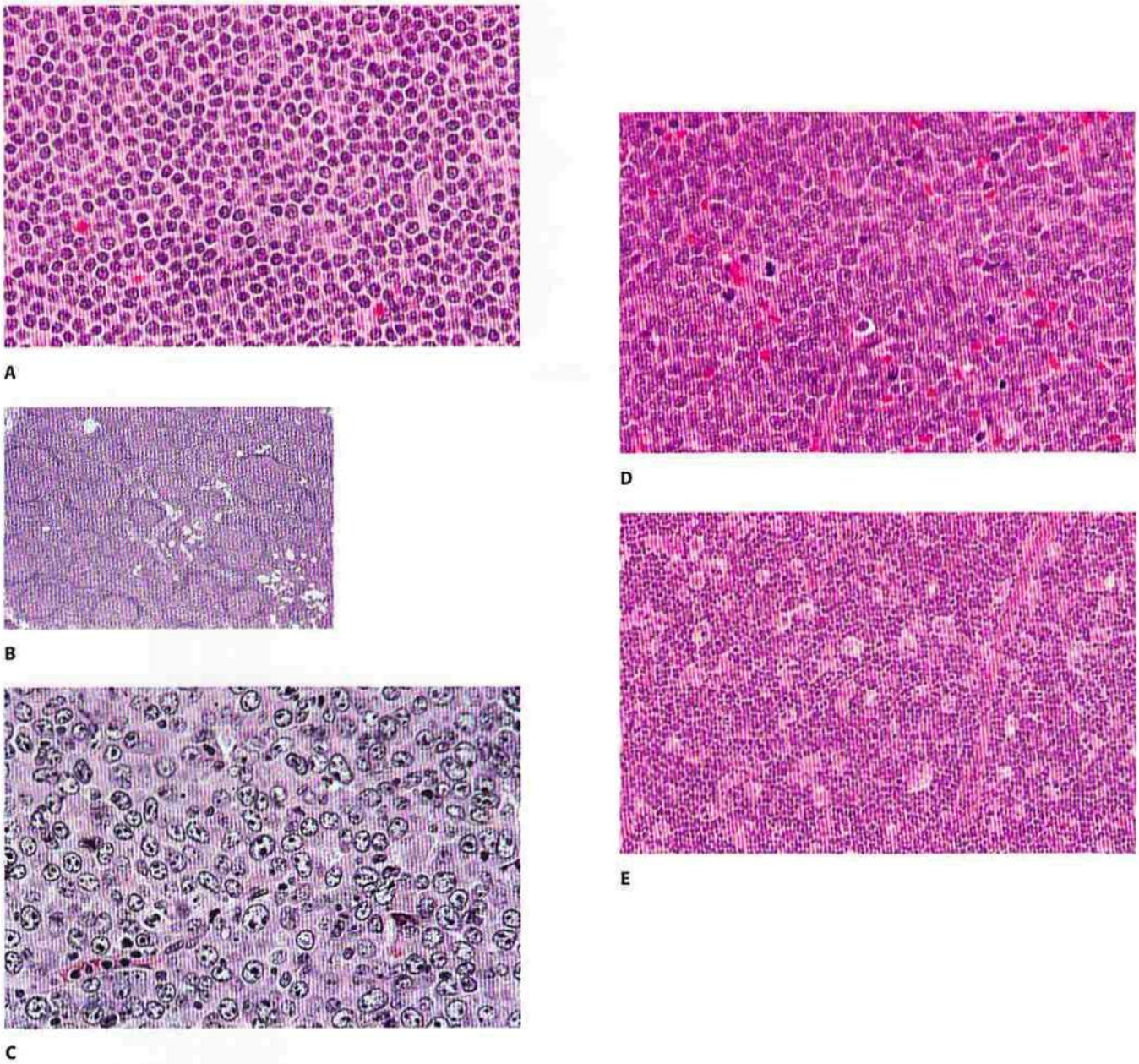


FIGURE 4-18. Histologic types of non-Hodgkin's lymphoma. (A) SLL; (B) follicular lymphoma (small cleaved cell); (C) diffuse large cell; (D) Lymphoblastic lymphoma; (E) Burkitt's lymphoma. (Parts A and C–E reproduced, with permission, from Lichtman MA, Beutler E, Kipps TJ, et al., *Williams Hematology*, 7th ed, New York: McGraw-Hill, 2006: Plates XXII-10, XXII-22, XXII-8, XXII-25; Part B reproduced, with permission, from Fauci AS, Braunwald E, Kasper DL, et al., eds. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008: Figure 105-7.)

Prognosis

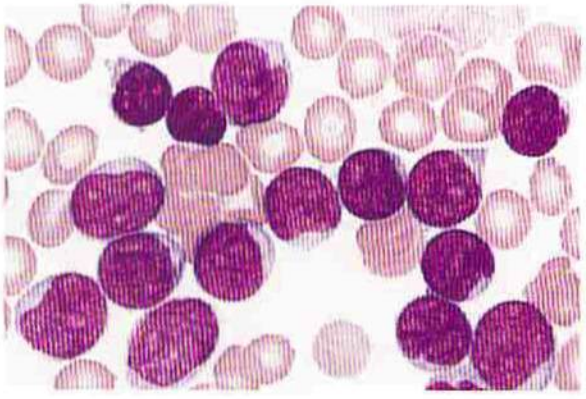
Almost all patients go into remission after chemotherapy, and in children about **two-thirds are cured**. This leukemia is the most responsive to therapy. Prognosis is worst for those under age 2, those who present in adolescence or later, and those with the Philadelphia translocation, t(9;22).

Chronic Lymphocytic Leukemia

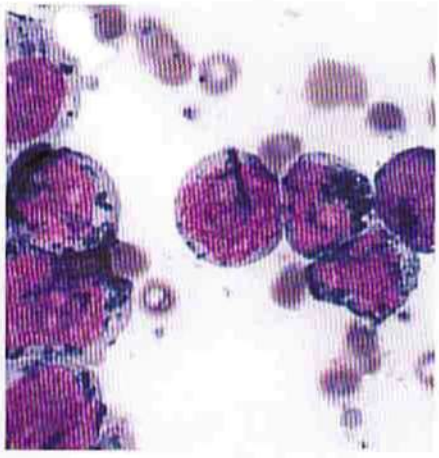
Neoplastic proliferation of lymphoid cells, usually **CD5+ B cells**. This disease is the same as **small lymphocytic lymphoma (SLL)** except that the majority of the neoplastic cells in CLL are in the circulation and marrow as opposed to only nodal or extranodal masses. Cells do not differentiate into antibody-secreting plasma cells.



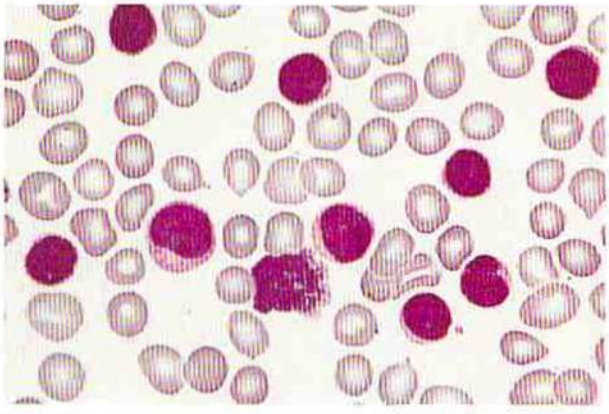
FIGURE 4-19. Mycosis fungoides. (Image courtesy of PEIR Digital Library [http://peir.net].)



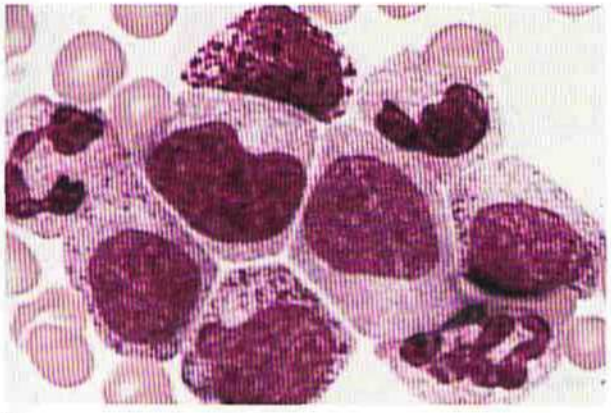
A



C



B



D

FIGURE 4-20. Peripheral smears of leukemias. (A) Acute lymphoblastic leukemia. Lymphoblasts have condensed chromatin with indented nuclei, minimal cytoplasm, and no granules. (B) Chronic lymphocytic leukemia. Small, round lymphocytes are visible in peripheral smears. Smudge cells, the result of the fragility of the neoplastic cells, are frequently seen. (C) Acute myelogenous leukemia. Myeloblasts with delicate chromatin, peroxidase-positive granules, and abundant cytoplasm compared to lymphoblasts. Cells in APL often contain Auer rods in the cytoplasm. (D) CML. Leukocytosis with a mix of neutrophils, metamyelocytes, and myelocytes, and less than 10% myeloblasts. Eosinophilia and basophilia are also common. (Reproduced, with permission, from Lichtman MA, Beutler E, Kipps TJ, et al., *Williams Hematology*, 7th ed, New York: McGraw-Hill, 2006: Plates XX-11, XX-4, XVI-3, and XIX-2.)

Presentation

Males are affected twice as often as females, and the average age of presentation is **60 years**. Patients are often asymptomatic or have nonspecific symptoms of weight loss and fatigue. Lymphadenopathy and hepatosplenomegaly are common. Bacterial infections are common as a result of hypogammaglobulinemia. Autoantibodies that develop in reaction to the tumor cells can lead to **warm antibody autoimmune hemolytic anemia** or thrombocytopenia. **Prolymphocytic transformation** into diffuse B-cell lymphoma occurs in one-quarter of cases.

Diagnosis

Small, round lymphocytes are visible in peripheral smears and bone marrow biopsies. **Smudge cells**, the result of the fragility of the neoplastic cells, are frequently seen. Some patients may have a monoclonal Ig "spike."

Prognosis

Survival is typically 4–6 years. If prolymphocytic transformation occurs, survival is less than 1 year.

Acute Myelogenous Leukemia

Acquired genetic mutations in stem cells lead to proliferation of undifferentiated myeloid blasts. Also known as acute granulocytic leukemia. Classified as arising from myelodysplasia, or de novo.

One specific type of acute myelogenous leukemia (AML) is **acute promyelocytic leukemia (APL)** which results from a translocation of the retinoic acid receptor-α (*RAR-α*) gene from chromosome 17 to next to the promyelocytic leukemia gene on chromosome 15 [t(15;17)(q22;q12)]. The result is an abnormal receptor that prevents cell differentiation and maturation.



MNEMONIC

Acute Promyelocytic Leukemia:

A pro's engine RARs (roars) at 1715 myels (miles) per Auer (hour).

Presentation

The de novo form affects **adults** (15–39 years old), but cases arising from myelodysplasia usually affect people in the sixth decade or beyond. Patients have symptoms of fatigue, infection, and bleeding because of anemia, neutropenia, and thrombocytopenia.

Diagnosis

Based on peripheral smear and bone marrow biopsy. Biopsy reveals > 20 myeloid blasts in marrow. On smear, myeloblasts have delicate chromatin, peroxidase-positive granules, and **abundant cytoplasm** compared to lymphoblasts.

Cells often contain **Auer rods** (peroxidase-positive cytoplasmic inclusions) in the cytoplasm, especially in APL. Surface markers can be assessed to differentiate from ALL.

Treatment

Chemotherapy; high-dose **all-trans-retinoic acid** can overcome the blockade caused by the abnormal protein in APL with a t(15;17) translocation.

Prognosis

Chemotherapy is successful in producing complete remission in approximately 60% of patients; however, more than half of these people have recurrence of disease within 5 years. Specific genetic alteration influences prognosis.

Remission also results in a large portion of patients treated with all-trans-retinoic acid, though relapse almost always occurs. Also of note, treatment of APL may release large numbers of Auer rods, which can result in DIC.

Chronic Myelogenous Leukemia

Proliferation of pluripotent cells producing myeloid cells which are capable of terminal differentiation; also known as **chronic myelocytic** or **chronic granulocytic leukemia**. Note that this is both a leukemia and a myeloproliferative disorder. Production of normal cells is prevented because of overcrowding. Cases are associated with the **Philadelphia (Ph) chromosome** as the ***c-abl*** gene is moved from **chromosome 9 to 22**, next to the ***bcr*** gene. The result is a fusion protein, ***BCR-ABL***, with tyrosine kinase activity that leads to uncontrolled proliferation.

Presentation

Insidious onset with non-specific symptoms such as mild anemia and weight loss, typically in middle-age patients. **Splenomegaly** is common. An **accelerated phase** with increasing anemia and thrombocytopenia often occurs after approximately 3 years. Whether or not there is an accelerated phase, all untreated patients eventually enter a **blast crisis with > 20% blasts on peripheral smear**, a condition similar to acute leukemia.

Diagnosis

Peripheral smear and bone marrow biopsy aid diagnosis, although chromosomal analysis or PCR can be used to definitively detect the ***BCR-ABL* fusion gene**. Leukocytosis with mixed neutrophils, metamyelocytes, myelocytes, and absolute basophilia on smear. The marrow is entirely filled with cells, especially mature granulocytic precursors. Can be differentiated from leukemoid reactions because **leukocyte alkaline phosphatase is not as elevated in chronic myelogenous leukemia (CML)**.

Treatment

- **Gleevec (imatinib mesylate)**: Induces apoptosis of leukemic cells; has almost completely replaced other therapies.
- **Low-dose chemotherapy**: Stabilizes early phase, but does not prevent accelerated phase and blast crisis.
- **Interferon-alfa.**
- **Allogenic bone marrow transplantation**: Cures up to 75% of cases, and is most effective in the stable phase.

FLASH FORWARD

Gleevec inhibits ***BCR-ABL*** tyrosine kinase to decrease proliferation and increase apoptosis.

Prognosis

With or without treatment, initial progression is slow until accelerated phase and blast crisis.

Myeloproliferative Syndromes

Neoplastic proliferation of myeloid stem cells. Includes CML, polycythemia vera, and essential thrombocythemia.

Polycythemia Vera

Neoplasm of multipotent myeloid stem cells leading to excessive production of **erythrocytes**, **granulocytes**, and **megakaryocytes**.

Presentation

Insidious onset at median age of 60. Erythrocytosis causes stagnation of blood flow and cyanosis. Increased risk of **bleeding and thrombosis** leads to deep venous thrombosis, myocardial infarction, ischemic and hemorrhagic stroke, Budd-Chiari syndrome, splenic infarction, and mesenteric infarction. Headache, pruritus, peptic ulceration, and hyperuricemia are common. Marrow often progresses to **spent phase** with prominent fibrosis, and as a result, extramedullary hematopoiesis occurs. The clinical picture of myelofibrosis with myeloid metaplasia develops. **Splenomegaly** may occur from congestion early on or as a result of extramedullary hematopoiesis.

Diagnosis

Increased hematocrit. Bone marrow is hypercellular until spent phase, when fibrosis is prominent. To differentiate from CML, leukocyte alkaline phosphatase levels are *elevated*, and PCR will not reveal the *BCR-ABL* gene.

Treatment

Involves frequent **phlebotomy** to maintain normal red cell mass and lengthens survival by approximately 10 years.

Prognosis

Without treatment, death occurs within months.

Myelofibrosis with Myeloid Metaplasia

Neoplastic changes in multipotent stem cells leads to proliferation of cells including megakaryocytes. The **megakaryocytes** release platelet-derived growth factor and transforming growth factor-β (TGF-β), which encourage growth of non-neoplastic fibroblasts. The fibroblasts produce significant amounts of collagen, and the result is **prominent fibrosis** occurring early in course of the disease (see Figure 4-21). Similar to the spent phase of polycythemia vera.

Presentation

Usually affects individuals **60+ years of age** who present with anemia, splenomegaly, nonspecific symptoms, and hyperuricemia (a result of high cell turn-

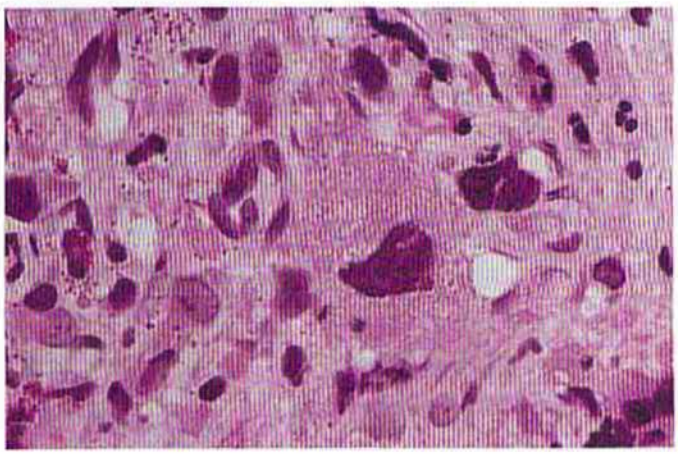


FIGURE 4-21. Myelofibrosis with myeloid metaplasia, bone marrow biopsy. (Reproduced, with permission, from Lichtman MA, Beutler E, Kipps TJ, et al., *Williams Hematology*, 7th ed, New York: McGraw-Hill, 2006: Plate XIV-11.)

over); also infection, bleeding, and thrombosis because of cell abnormalities. Marrow fibrosis necessitates extramedullary hematopoiesis which results in hepatosplenomegaly.

Diagnosis

Marrow is initially hypercellular, but progressively becomes hypocellular and fibrotic. Eventually, the marrow is converted to bone by osteosclerosis. Peripheral smear shows **leukoerythroblastosis**, increased numbers of nucleated erythroid progenitors and early granulocytes, as fibrosis leads to the abnormal release of these cells. **Teardrop erythrocytes**, or **dacrocytes**, are common as well. Lab tests reveal normochormic normocytic anemia and thrombocytopenia as the disease advances.

Prognosis

Survival ranges from 1–15 years.

Essential Thrombocythemia

Neoplastic proliferation of myeloid stem cells which leads to production of megakaryocytes.

Presentation

Indolent course, usually asymptomatic except for episodes of prominent thrombosis and hemorrhage.

Diagnosis

Marrow is moderately hypercellular, and large numbers of normal and **abnormally large megakaryocytes** are seen. No fibrosis develops. Peripheral smear shows extremely large platelets.

Prognosis

Survival is approximately 5–30 years.

Plasma Cell Disorders

Include multiple myeloma, Waldenström's macroglobulinemia, and monoclonal gammopathy of undetermined significance. These disorders are caused by clonal neoplastic transformation of Ig-secreting, terminally differentiated B cells. Monoclonal Ig is referred to as the **M component**. The balance between light-chain and heavy-chain production is lost, and free light chains, **Bence Jones proteins**, are excreted in the urine.

Multiple Myeloma

Neoplastic proliferation of small lymphoid cells leads to clonal expansion of plasma cells. A prominent feature is elevation in the levels of interleukin-6, which is an osteoclast-activating factor.

Presentation

Usually presents in patients **50–60 years old**. Characteristics include:

- **Punched-out bone lesions**, especially in the vertebrae and skull. Fractures of the vertebral column and bone pain are common.
- **Hypercalcemia** from bone destruction.
- **Myeloma kidney**, or renal insufficiency with azotemia, because of excretion of Bence Jones proteins; tubular casts of Bence Jones protein, giant cells, and metastatic calcification may be evident.

- **Marrow failure** leading to anemia, and rarely leukopenia and thrombocytopenia.
- **Infections,** especially with *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *E. coli*, as a result of clonal Ig, leading to decreased production of normal Ig.
- **Amyloidosis.**
- **Hyperviscosity syndrome** in a minority of cases.

Diagnosis

Hyperglobulinemia may lead to **rouleaux formation** of red cells (an aggregate of erythrocytes stacked like a pile of coins). Electrophoresis usually reveals increased Ig in blood and/or Bence Jones proteins in the urine. **IgG** is the M component in about half of cases; IgA in about one-quarter. X-rays usually reveal **punched-out round skeletal lesions**, but sometimes the presentation is of generalized osteoporosis. Cells have a characteristic "**fried-egg**" appearance (see Figure 4-22).

Prognosis

Survival is variable with an average of **3–5 years**. Some forms are indolent, while others have a survival of 6–12 months. Death usually occurs from infection or renal insufficiency. Chemotherapy leads to remission in about half of patients. **Bisphosphonates** can inhibit bone resorption. Bone marrow transplantation can improve survival but is not a cure.

Waldenström's Macroglobulinemia

Neoplasm of **plasmacytoid lymphocytes** (cells between B lymphocytes and plasma cells in terms of maturity) with monoclonal **IgM** secretion. Also known as lymphoplasmacytic lymphoma.

Presentation

Typically affects **50+-year-old males**. Nonspecific symptoms of fatigue and weight loss are common, as are lymphadenopathy, hepatomegaly, and splenomegaly. Anemia occurs as a result of marrow failure and sometimes because of IgM **cold antibody autoimmune hemolysis**. **Hyperviscosity syndrome** often develops and presents with visual impairment such as retinal vascular dilation, neurologic issues, bleeding, and Raynaud's phenomenon.

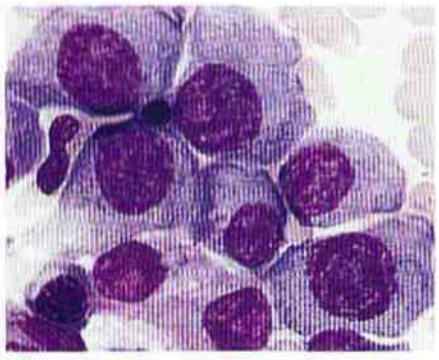


FIGURE 4-22. Multiple myeloma. (Reproduced, with permission, from Lichtman MA, Beutler E, Kipps TJ, et al., *Williams Hematology*, 7th ed, New York: McGraw-Hill, 2006: Plate XXI-4.)

Diagnosis

Electrophoresis of serum reveals a clonal IgM spike, and 10% of cases show Bence Jones proteinuria; no bone lesions.

Prognosis

Incurable and progressive with a median survival of 4 years. Plasmapheresis can treat hyperviscosity and hemolysis. Rarely transforms to large-cell lymphoma.

Monoclonal Gammopathy of Uncertain Significance

Some healthy, older adults may have benign M proteins with no symptoms or disease. Some, however, may go on to develop multiple myeloma or other plasma cell dyscrasias after 10–15 years. Amyloidosis can also develop.

Langerhans' Cell Histiocytosis

Histiocytosis refers to the proliferation of histiocytes or macrophages. In Langerhans' cell histiocytosis there is a clonal proliferation of **dendritic cells** known as Langerhans 'cells.

Presentation

Typical presentations include:

- **Letterer-Siwe disease:** Acute disseminated histiocytosis; usually before age 2 years; characterized by cutaneous lesions on trunk and scalp; marrow failure, hepatosplenomegaly, and osteolytic lesions develop.
- **Eosinophilic granuloma:** Unifocal or multifocal expansion of Langerhans' cells, usually in marrow space and occasionally in lung; asymptomatic or with pain and possibly fractures.
- **Multifocal Langerhans' cell histiocytosis:** Affects children; fever, eruptions on the scalp and in the ear canals, recurrent infections, hepatosplenomegaly, and diabetes insipidus from posterior pituitary involvement; calvarial lesions, diabetes insipidus, and exophthalmos define **Hand-Schüller-Christian** disease.

Diagnosis

Electron microscopy reveals **Birbeck's granules** in cytoplasm which appear like **tennis racquets**. Immunohistochemical techniques aid diagnosis.

Prognosis

Depends on type. The acute disseminated presentation is rapidly fatal if untreated; with chemotherapy, half survive for about 5 years. Unifocal lesions can be excised or irradiated and occasionally heal without treatment. Multifocal histiocytosis can be treated with chemotherapy, though this may also heal without treatment. It has a better prognosis than the acute disseminated form.

Heme Pathology

Heme production occurs via the synthetic pathway shown in Figure 4-23. A defect in any of these steps can result in **porphyrias**, a group of diseases that result from the accumulation of heme intermediates.

Acute Intermittent Porphyria (AIP)

Autosomal-dominant, leading to a deficiency in porphobilinogen deaminase with subsequent accumulation of upstream metabolites–**porphobilinogen**

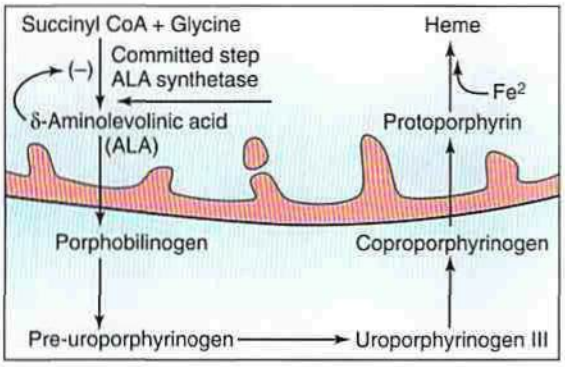


FIGURE 4-23. Heme synthesis. Underproduction of heme results in a microcytic hypochromic anemia. Accumulation of intermediates causes pophyrias.

(**urinary**), and **δ-aminolevulinic acid** (**ALA**). These intermediates lead to degeneration of myelin.

Presentation

May be induced by sun exposure and certain medications (sulfa drugs, and barbiturates, in addition to *many* others). Symptoms include dark, foul colored urine, hallucinations, blurred vision, and gross neurological manifestations such as foot drop.

Diagnosis

Genetic testing, increased urinary secretion of porphobilinogen, and porphyrins is pathognomonic. Measuring the activity of porphobilinogen deaminase is of little value, as some patients will have normal levels.

KEY FACT

AIP differs from other porphyrias because it has no sun-induced lesions.

Treatment

Goal is to decrease heme synthesis, thereby reducing production of porphyrin precursors. Patients should eat a high-carbohydrate diet during acute attacks. Severe attacks should be treated with hematin.

Porphyria Cutanea Tarda (PCT)

Part of the porphyria spectrum that results from deficient activity of the heme synthetic enzyme uroporphyrinogen decarboxylase (UROD). This leads to elevated porphyrin by-products, including elevated **uroporyphyrin**, iron, and transferrin.

Pathology

Accumulation of iron leads to siderosis, affecting liver function. Accumulated uroporyphyrins lead to bullae and skin lesions which form upon exposure to sunlight.

Presentation

Patients present with cutaneous bullae which form upon exposure to sunlight. Additional organ damage includes liver siderosis and eventual fibrosis. Urine turns dark upon standing. The disease is exacerbated by consumption of alcohol, iron, and estrogens.

TABLE 4-8. Summary of the Porphyrias

Disease	Deficit	Presentation	Treatment
Acute intermittent porphyria	Porphobilinogen deaminase	Dark, foul smelling urine, neurological deficits (usually following sun exposure or certain medications).	Hematin, high carbohydrate diet.
Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	Bullae on sun-exposed areas, liver siderosis, dark urine upon standing.	Low-dose antimalarials, phlebotomy. Avoidance of alcohol, sun-exposure, estrogens and iron.

Diagnosis

Plasma and urine analysis for elevated uroporyphyrin. The activity of the uroporphyrinogen decarboxylase (UROD) can also be tested in red blood cells.

Treatment

- Low-dose antimalarial medications, phelebotomy.

The porphyria syndromes are summarized in Table 4-8.

Pharmacology

CHEMOTHERAPY DRUGS: ALKYLATING AGENTS

These drugs are cell-cycle nonspecific. They act by interfering with nucleic acid function in various ways (e.g., by cross-linking DNA, by promoting incorrect base pairing, and sometimes causing DNA strand breaks).

Cyclophosphamide and Ifosfamide

Mechanism

Covalently cross-link DNA at guanine N-7. They require activation by the CYP-450 enzyme system in the liver.

Uses

NHL, breast and ovarian cancer.

Side Effects

Toxic metabolite is acrolein, which causes **hemorrhagic cystitis**. This can be prevented by **co-administration of mesna**. Other side effects include myelosuppression and extreme nausea.

Nitrosureas (Carmustine, Lomustine, Streptozocin)

Mechanism

These agents require bioactivation. They are able to **cross the blood-brain barrier**, because they are very **lipid soluble**. Therefore, they are used for **CNS tumors**.

Uses

Brain tumors, especially glioblastoma multiforme.

Side Effects

CNS toxicity including dizziness and ataxia. Also extreme nausea.

Cisplatin and Carboplatin

Mechanism

Cross-link DNA strands, thus inhibiting DNA replication.

Uses

Testicular, bladder, ovarian, and lung cancer.

Side Effects

Nephrotoxicity, neurotoxicity, ototoxicity. Also extreme nausea.

Busulfan

Mechanism

Alkylates DNA and interferes with function.

Uses

CML.

Side Effects

Pulmonary fibrosis, hyperpigmentation.

KEY FACT

Most alkylating agents cause severe nausea.

ANTIMETABOLITES

These drugs are cell-cycle–specific (predominantly for S phase). They structurally resemble purines, pyrimidines, or other endogenous compounds. However, they are nonfunctional, so they block nucleic acid synthesis.

Methotrexate

Mechanism

Folic acid analog that inhibits the enzyme dihydrofolate reductase. This results in decreased DNA and protein synthesis. It is specific for the synthesis phase (S phase) of the cell cycle.

Uses

Leukemias, lymphomas, sarcomas, choriocarcinoma. Also used for abortion, ectopic pregnancy, rheumatoid arthritis, Crohn's disease, psoriasis.

Side Effects

Myelosuppression, which is reversible with **leucovorin** (folinic acid). Also causes fatty change in liver (like ethanol and amiodarone).

6-Mercaptopurine (6-MP)

Mechanism

Blocks purine synthesis. Must be activated by hypoxanthine guanine phosphoribosyl transferase (HGPRTase).

Uses

Leukemias, lymphomas.

Side Effects

Myelosuppression. 6-MP is **metabolized by xanthine oxidase**, so increased toxicity is seen with co-administration of allopurinol (xanthine oxidase inhibitor).

Cytarabine

Mechanism

Pyrimidine antagonist, terminates chain elongation. Also inhibits DNA polymerase.

Uses

Acute myelogenous leukemia.

Side Effects

Leukopenia, thrombocytopenia, megaloblastic anemia.

5-Fluorouracil (5-FU)

Mechanism

Pyrimidine analog that is bioactivated to 5-fluoro-deoxyuridine monophosphate (5F-dUMP). 5F-dUMP binds folic acid, and this complex **inhibits thymidylate synthase**. The result is inhibited nucleic acid synthesis. It is S-phase specific.

Uses

Colorectal cancer and other solid tumors. Used topically for basal cell carcinoma of the skin.

Side Effects

Myelosuppression, "hand-foot syndrome" (dermopathy after extended use).

TOPOISOMERASE INHIBITORS

Etoposide, Doxorubicin, and Irinotecan

Mechanism

Inhibit topoisomerases (I or II), thus preventing DNA replication and inducing DNA double-strand breaks.

Uses

Breast, thyroid, ovarian, and testicular cancer; lymphoma.

Side Effects

Doxorubicin has cardiac side effects including myopathy, failure, and arrhythmias. Irinotecan causes severe diarrhea.

DRUGS THAT TARGET TUBULIN

Vincristine and Vinblastine

Mechanism

Prevent microtubule formation by interfering with tubulin binding. The mitotic spindle cannot form, and the M phase does not proceed.

Uses

Lymphomas, testicular cancer, small-cell lung cancer.

Side Effects

ViNcristine causes Neurotoxicity. VinBlastine causes Bone marrow toxicity.

Paclitaxel

Mechanism

Prevents microtubule breakdown by stabilizing tubulin already bound in mitotic spindles. M phase cannot complete.

Uses

Ovarian, breast, non-small-cell lung, bladder, head and neck cancer.

Side Effects

Acute hypersensitivity reaction, neurotoxicity.

KEY FACT

Although these drugs act in opposite ways, they achieve the same effect: inhibition of a full cycle of mitosis.

HORMONAL AGENTS

Tamoxifen, Letrozole, and Raloxifene

Mechanism

Antiestrogens, these block estrogen production or competitively inhibit the estrogen receptor present on some cancer cells. This decreases DNA synthesis.

Uses

Estrogen-sensitive breast cancers, especially in postmenopausal women. Raloxifene additionally stimulates the bone to increase density.

Side Effects

Tamoxifen activates estrogen receptors on other types of tissue such as endometrium, increasing endometrial cancer risk. All can cause mild hot flashes and nausea.

Leuprolide and Goserelin

Mechanism

Agonists of luteinizing hormone-releasing hormone (LHRH). Shuts off LH release when given continuously, thereby inhibiting testosterone or estrogen production.

Uses

Prostate cancer, breast cancer in premenopausal women.

Side Effects

Early acute exacerbation of prostate cancer.

TARGETED MOLECULAR THERAPEUTICS

Trastuzumab

Mechanism

Antibody against erb-B2 may facilitate T-cell cytotoxicity against cancer cells with erb-B2 expression.

Uses

Breast cancers that express erb-B2 (~ 30%).

Side Effects

Cardiotoxicity, especially when combined with doxorubicin.

Imatinib

Mechanism

Inhibits BCR-ABL tyrosine kinase specific to CML.

Uses

CML.

Side Effects

Mild.

NATIVE CYTOKINES USED IN CANCER TREATMENT

Interferon-Alfa

Mechanism

Enhances cell-mediated immunity against some cancers and viruses, possibly by upregulating expression of antigen in tumor cells. May also have direct apoptotic activity.

Uses

Hemangiomas, advanced melanoma, renal tumors; also hepatitis C.

Side Effects

Depression and flulike symptoms.

Interleukin-2

Mechanism

Stimulates T-cell survival and activation, enhancing cell-mediated immunity against cancer cells.

Uses

Kidney cancers and melanoma.

Side Effects

Capillary leak syndrome (hypotension, low vascular resistance, and high cardiac output similar to septic shock).

Rapid Review

Key Terms

Anemia	Reduction in the O_2-transporting capacity of blood, usually because of a reduction of the total circulating RBC mass to below-normal levels.
Anisocytosis	Abnormal size variation among RBCs.
Haptoglobin	A protein that binds free hemoglobin in the serum. It is decreased in hemolytic anemias.
Hematocrit	Represents the percentage of whole blood volume composed of erythrocytes.
Mean cell hemoglobin	The average content of hemoglobin per RBC.
MCHC	The average concentration of hemoglobin in a given volume of packed RBCs. The MCHC is low if the RBCs are hypochromic.
MCV	The average volume of an RBC. A normal value is 80–100 fL. Over 100 fL would be a macrocytic anemia, while under 80 fL would be microcytic.
Normoblast	Nucleated RBC (in peripheral blood reflects hyperplasia of erythroid progenitors).
Normocytic, microcytic, macrocytic	All of these refer to the size of the RBCs: normocytic refers to a normal-sized RBC, microcytic to a small RBC, and macrocytic to a large RBC.
Normochromic, hypochromic	These terms refer to the color of RBCs, which is a sign of the amount of hemoglobin in the RBCs. Normochromic is normal and hypochromic is a pale color (which correlates to low hemoglobin).
RBC distribution width (RDW)	The coefficient of variation of RBC volume. An increased RDW means that the RBCs are extremely variable in size.
Reticulocytosis	Increased number of newly formed RBCs in the peripheral blood.
Ineffective erythropoiesis	RBC inclusions results in destruction of young RBCs within the bone marrow (intramedullary destruction). A condition often seen in thalassemia.

"PLASIA" DEFINITIONS

Implying growth or development. Tissue can grow by different mechanisms, each known by a different term:

- **Hyperplasia:** Overactive growth of a tissue.
- **Neoplasia:** Means "new growth." Refers to cancer tissue and fundamentally infers a loss of responsiveness to normal growth control signals.
- **Dysplasia:** Abnormal growth of a tissue, disordered, but not neoplastic.
- **Metaplasia:** Transformation of tissue from one type to another.
- **Anaplasia:** Malignant transformation of undifferentiated cells.

TUMOR NOMENCLATURE

Tumors are often first defined by their "aggressiveness" and ability to metastasize (spread to other sites beyond the primary site) to other sites.

Benign

Tumor shows microscopic and gross evidence that it will remain localized and not metastasize. Implies it is amenable to surgical resection.

- **Fibroma:** A benign neoplasm of fibrous or connective tissue.
- **Chondroma:** A benign neoplasm of cartilaginous cells.
- **Adenoma:** A benign neoplasm of glandular cells.
- **Papilloma:** A benign neoplasm of epithelial tissue that typically has a stalk or pedicle.
- **Polyps:** Similar to a papilloma, any growth, benign or malignant, that has a stalk or pedicle.
- **Cystadenoma:** A neoplasm of epithelial glandular origin but with production of a substrate producing cysts within the neoplasm.

Malignant

"Cancers." Tend to adhere, infiltrate, and destroy surrounding tissue. Prone to metastasize to distant sites.

- **Sarcomas:** Malignant tumors arising from mesenchymal tissue.
- **Carcinomas:** Malignant tumors of epithelial origin.
- **Teratoma:** Tumors that contain more than one germ cell layer and typically contain immature and mature elements.
- **Hamartoma:** Mass of disorganized tissue elements, not necessarily a neoplasm.

TUMOR GRADE VERSUS STAGE

Grading and staging of tumors guides medical and surgical therapy and provides information on prognosis.

Grading

Based on the microscopic appearance of a tumor it can be graded 1–4 in levels of increasing severity and differentiation. Well-differentiated tumors are grade 1 and tend to be less aggressive. Grade 4 tumors tend to be poorly differentiated and highly aggressive.

Staging

The extent to which a primary tumor has spread, which helps determine treatment and prognosis. Typically described in the TNM staging system, which refers to (T) Tumor: the extent of tumor growth; (N) Nodes: which and how many lymph nodes are involved; and (M) Metastasis: has the tumor metastasized.

PSAMMOMA BODIES

Histologically seen as laminated, concentric, calcified spheres found in several types of cancer.

- **Thyroid papillary adenocarcinoma:** Patient presents with a solitary thyroid nodule. May have an enlarging neck mass. Fine-needle aspiration of the nodule shows finger-like projections composed of tumor cells lining a core of fibrous tissue.
- **Meningioma:** Arises from the dura. May present with focal neurologic deficit, headaches, or seizures.
- **Malignant mesothelioma:** Arises from the pleural surface. Look for dyspnea, atypical chest pain, exposure to asbestos, and cigarette smoking.
- **Serous papillary cystadenocarcinoma of the ovary.**

ONCOGENES

Genes derived from mutations in "protooncogenes" to "oncogenes," which promote cell growth in cancer cells. All oncogenes contribute to persistent expression of cellular growth factors (e.g., cyclin-dependent kinases).

- ***MYC* gene:** Oncogene most commonly found in human tumors.
- **Others:** *MYB*, *JUN*, *FOS*, and *REL* oncogenes.

TUMOR SUPPRESSOR GENES

Genes that suppress continued cell growth. Inhibition of these genes makes cells refractory to inhibition of growth.

- **Retinoblastoma (RB):** First tumor suppressor gene to be discovered. Retinoblastoma is a neoplasm of the retina that typically occurs in young children with an abnormal *Rb* gene located on chromosome 13. Findings include leukocoria and loss of red light reflex in infants.
- **Others:** *APC* gene, TGF-β, and *TP53*.
- **Two-hit hypothesis:** In order for a tumor suppressor gene to be rendered inactive both normal alleles must be inactive.

ONCOGENIC VIRUSES

Viral infection of cells can lead to unchecked proliferation and tumor development (see Table 4-9).

PARANEOPLASTIC SYNDROMES

Complex of symptoms that cannot be explained by the spread of tumor cells. Occur in 10%–15% of cancer patients. Certain cancers will cause specific paraneoplastic syndromes (see Table 4-10).

TABLE 4-9. Oncogenic Viruses

Human T-cell leukemic virus type 1	RNA oncogenic virus. Associated with T-cell leukemia and lymphoma.
Epstein-Barr virus	DNA oncogenic virus. Associated with Burkitt's lymphoma, AIDS-related lymphomas, Hodgkin's lymphoma.
Human papillomavirus	DNA oncogenic virus. Associated with cervical carcinoma.
Human herpesvirus-8	DNA oncogenic virus. Associated with Kaposi's sarcoma.
Hepatitis B virus	DNA oncogenic virus. Associated with hepatocellular carcinoma.

RED BLOOD CELL FORMS

Various diseases can cause the RBCs to take different shapes. Knowing these different forms helps in elucidating the underlying disease (see Table 4-11).

ANEMIA AND RED BLOOD CELLS

A decrease in the effective O_2-carrying capacity of RBCs. These can be categorized by the morphology of the RBCs (see Table 4-12).

IRON DEFICIENCY ANEMIA

Most common form of nutritional deficiency. Negative iron balance may result from low dietary intake, malabsorption, excessive demand (pregnancy and infancy), and chronic blood loss (heavy menses or gastric ulcers).

TABLE 4-10. Paraneoplastic Syndromes

Cushing's syndrome	Small cell cancer of the lung, pancreatic carcinoma.
SIADH	Small cell cancer of the lung, intracranial neoplasm.
Hypercalcemia	Squamous cell cancer of the lung, breast cancer, renal cell carcinoma.
Myasthenia gravis	Thymoma.
Hypertrophic osteoarthropathy	Lung cancer.
Migratory venous thrombosis	Trousseau's syndrome, pancreatic carcinoma.
Cancer cachexia	Progressive loss of lean body mass and body fat, weakness, anorexia, and anemia.

TABLE 4-11. Red Blood Cell Forms

Biconcave	Normal
Spherocytes	HS, autoimmune hemolysis.
Macrocyte	Megaloblastic anemia.
Helmet cell/schistocyte	DIC, traumatic hemolysis.
Sickle cell	Sickle cell anemia.
Teardrop cell	Myelofibrosis.
Acanthocyte	Abetalipoproteinemia.
Target cell	Thalassemia, liver disease, hemoglobin C, asplenia.
Poikilocytes	TTP/ HUS, microvascular hemolysis, DIC.
Burr cell	TTP/HUS.

Decrease in serum iron and increase in TIBC. Leads to hypochromic and microcytic RBCs.

- **Ferritin:** Serum ferritin is a good indicator of the adequacy of bone iron stores.
- **Transferrin:** Iron is transported in the blood by transferrin (protein).
- **Atrophic glossitis:** Smooth, glazed appearance of the tongue.
- **Plummer-Vinson syndrome:** Occurs in iron-deficiency anemia when atrophic glossitis coexists with dysphagia and esophageal webs.
- **Pica:** Eating of unusual substances or odd cravings. Desire to eat dirt or clay or chew ice.

TABLE 4-12. Morphologic Categorization of Anemias

Type	Etiology	Manifestations
Microcytic, hypochromic (MCV <80 fL)	Iron deficiency, thalassemia target cells, lead poisoning.	Elevated TIBC, decreased ferritin and serum iron.
Macrocytic (MCV >100 fL)	Megaloblastic folate/vitamin B_{12} deficiency, drugs that block DNA synthesis.	Hypersegmented neutrophils, neurologic abnormalities in vitamin B_{12} deficiency.
Normocytic, normochromic	Acute hemorrhage, G6PD deficiency, HS, bone marrow disorders, hemoglobinopathies, autoimmune hemolysis, anemia of chronic disease.	Decreased TIBC and serum iron, elevated ferritin, decreased serum haptoglobin in hemolysis.

ANEMIA OF CHRONIC DISEASE

Most common form of anemia in hospitalized patients. Caused by inflammation-induced sequestering of iron within the cells of the reticuloendothelial system. Increased stored iron in marrow macrophages.

- **Labs:** High serum ferritin, low TIBC.

MEGALOBLASTIC ANEMIA

Caused by folate deficiency or vitamin B_{12} deficiency causing abnormal DNA synthesis. The hallmark of megaloblastic anemia is enlargement of erythroid precursors which give rise to large RBCs (macrocytes). Bone marrow is hypercellular.

- **Hypersegmented neutrophils:** Produced by giant metamyelocytes. Nuclei contain more than five lobes.
- **Nuclear-cytoplasmic asynchrony:** DNA development is affected, and does not continue at the same pace as RNA and cytoplasmic protein synthesis.
- **Cheilosis:** Fissures or scales around the mouth and lips.
- **Folate deficiency:** Associated with poor diet, inhibited absorption, or increased metabolic needs (celiac disease). Unlike vitamin B_{12} deficiency, there are no neurologic abnormalities.
- **Vitamin B_{12} (cobalamin) deficiency:** Causes anemia associated with demyelination of the peripheral nerves and ultimately spinal cord (posterior and lateral columns). Patients report neurologic deficits.

PERNICIOUS ANEMIA

Vitamin B_{12} deficiency resulting from inadequate gastric production or defective function of intrinsic factor (IF; produced by the stomach, binds to vitamin B_{12}, and allows for absorption in the terminal ileum) necessary to absorb vitamin B_{12}. Several abnormalities along this pathway can lead to pernicious anemia.

- **Parietal canalicular antibody:** Causes deranged synthesis of IF by binding to mucosal parietal cells of the stomach.
- **Blocking antibody:** Blocks binding of vitamin B_{12} to IF.
- **Binding antibody:** Reacts with the IF-B_{12} complex and prevents it from binding to ileal receptors.
- **Gastrectomy:** Removal of a portion of stomach. May take the parietal cells that synthesize IF.

MYELOPHTHISIC ANEMIA

Marrow failure caused by extensive replacement of the marrow by tumor or other lesions.

- **Associations:** Metastatic cancer arising from breast, lung, prostate, or thyroid.
- **Presentation:** Anemia and thrombocytopenia.
- **RBCs:** Teardrop cells seen on PBS.

APLASTIC ANEMIA

Suppression of multipotent myeloid stem cells in the bone marrow with resultant anemia, thrombocytopenia, and neutropenia (pancytopenia); > 50% of cases are idiopathic. Other etiologies include certain myelotoxic agents and postviral infections (hepatitis and parvovirus in sickle cell patients).

- **Presentation:** Classic presentation of a sickle cell patient with recent illness causing fatigue, weakness, petechiae, and frequent infections.
- **Physical exam:** No splenomegaly.
- **Bone marrow biopsy:** Hypocellular bone marrow and increased amount of fat.
- **Thrombocytopenia:** Presents as the appearance of petechiae and ecchymoses due to low platelet count.
- **Granulocytopenia:** Low white blood cell count manifested by frequent or persistent minor infections or the sudden onset of chills, fever, and prostration.

HEMOLYTIC ANEMIA

Anemia associated with decreased RBC life-span (< 120 days). Shortened life-span may be the result of defects in the RBC (intracorpuscular) or external to the RBC (extracorpuscular). The increased RBC destruction results in reticulocytosis. The location of RBC destruction determines the presentation.

- **Intravascular hemolysis:** RBC destruction within the vasculature releasing hemoglobin with subsequent hemoglobinuria and jaundice. Haptoglobin binds free hemoglobin and is thus low. One of the more serious complications of massive hemolysis is acute tubular necrosis.
- **Extravascular hemolysis:** Occurs within the spleen or liver secondary to RBC injury or immunologic alteration. RBCs are altered, impairing passage through the spleen or liver, resulting in phagocytic destruction. Does not result in hemoglobinuria but can result in jaundice. Haptoglobin is decreased. Splenomegaly is a common finding. As RBCs are destroyed, increased amounts of iron accumulate, resulting in hemosiderosis.

HEMOLYTIC ANEMIAS

Autoimmune Hemolytic Anemia

Autoantibodies target RBC membranes. Diagnosis is confirmed by the **Coombs antiglobulin test**.

- **Warm antibodies:** Due to IgG, which is active at 37°C, and in 25% of cases is associated with an underlying disease such as SLE.
- **Cold antibodies:** Due to IgM, which is active below 37°C and is associated with mycoplasma infections, infectious mononucleosis, and lymphoid neoplasms.

Hereditary Spherocytosis (HS)

Abnormal RBC structural protein (spectrin), which normally stabilizes the RBC membrane. Spherical RBCs are less deformable and more likely to be sequestered by the spleen. Manifests as anemia, jaundice, and splenomegaly.

- *PIGA* **gene:** Abnormal gene inherited in an autosomal dominant pattern.
- **Osmotic fragility test:** RBCs show increased fragility.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Rare, inherited disorder resulting in an abnormal PIG protein. RBCs are more sensitive to complement-induced lysis. Patients are at greater risk of infections and thrombosis.

- **History:** Dark urine (hemoglobinuria) in the morning from hemolysis throughout the day and night.

Microangiopathic

RBC destruction as a result of narrowed vessels secondary to another disease process. As RBCs move through the abnormal vessels they undergo stress, resulting in alteration in RBC membranes seen as schistocytes, burr cells, and helmet cells, resulting in splenic sequestration.

- **Disseminated intravascular coagulation (DIC):** Fibrin deposits can narrow vessels resulting in hemolysis.
- **Other etiologies:** Malignant hypertension, TTP, SLE, HUS, and malignancy.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

Enzymatic abnormality that reduces the RBC ability to prevent oxidative injury.

- **Heinz body:** Denatured hemoglobin that precipitates within the RBC.
- **Bite cell:** Splenic phagocytes try to "bite out" the Heinz body inclusions.

DISSEMINATED INTRAVASCULAR COAGULATION

Activation of the coagulation cascade with subsequent formation of thrombi. Platelets and coagulation factors are consumed with secondary activation of fibrinolysis. Patients will be coagulopathic and have thrombocytopenia, low-clotting factors, and elevated fibrin split products. Frequently results as a complication of another disease process.

- **Common etiologies:** Obstetric complications, sepsis, malignancy, and major trauma.

TESTS OF BLEEDING DISORDERS

A Group of diseases characterized by impaired ability to stop bleeding. Certain tests help determine the underlying etiology.

- **Bleeding time:** Time (in minutes) taken for a standardized skin puncture to stop bleeding. Tests platelet function. Prolonged if platelet abnormality is present.
- **Prothrombin time (PT):** Tests the adequacy of the extrinsic and common coagulation pathways. Prolonged when deficient in factors V, VII, or X, prothrombin, or fibrinogen.
- **Partial thromboplastin time (PTT):** Tests the adequacy of the intrinsic pathway. Prolonged in heparin therapy.
- **Mixing studies:** In cases in whom bleeding is prolonged, the patient's blood is mixed with blood that contains all the factors necessary for clotting. If the bleeding time corrects, the patient has a deficiency in one or more clotting factors. If the bleeding time does not correct, the patient has antibody to one or more clotting factors.

THROMBOCYTOPENIA

Platelet count <100,000/mm^3. Testing shows prolonged bleeding time with normal PT and PTT. May result from decreased production (bone marrow failure) or increased destruction (immune or non–immune mediated). Non–immune-mediated causes include DIC and prosthetic heart valves. Immune-mediated thrombocytopenia occurs secondary to antiplatelet antibodies.

Idiopathic Thrombocytopenic Purpura (ITP)

Antiplatelet antibodies and destruction of platelets within the spleen. Patients present with petechiae, epistaxis, easy bruising, bleeding after minor trauma, and gum bleeding. Associated with autoimmune disorders such as SLE, as well as viral infections and lymphoma. Splenectomy is curative in two-thirds of patients.

Thrombotic Thrombocytopenic Purpura (TTP)

TTP is associated with a lack of a metalloproteinase enzyme which normally degrades vWF. Without this enzyme vWF accumulates, resulting in platelet aggregation. Presents with the classic pentad of fever, anemia, thrombocytopenia, renal failure, neurologic deficits. More common in women.

- **Hemolytic uremic syndrome (HUS):** Similar to TTP without neurologic deficit or renal failure. Typically follows *E. coli* infection secondary to Shiga toxin damage to the endothelium. More frequent in children.

Heparin-Induced Thrombocytopenia (HIT)

Acquired IgG antibodies to platelet factor IV/heparin complexes. Antibody binding actually results in thrombosis despite thrombocytopenia. Occurs in 3%–5% of patients anticoagulated with heparin. Cessation of therapy is curative.

Bernard-Soulier Disease

Defect of platelet adhesion.

Glanzmann's Thrombasthenia

Defect of platelet aggregation.

COAGULOPATHIES

Result of congenital or acquired abnormalities in clotting factors. Acquired diseases include vitamin K deficiency and liver disease, both of which impair synthesis of factors VII, IX, and X. Hereditary diseases include hemophilia and von Willebrand's disease.

Hemophilia A

An X-linked recessive deficiency of factor VIII. Patients show a predisposition to easy bruising, excessive bleeding after trauma, and spontaneous bleeding into joints (hemarthrosis). No petechiae. Studies show prolonged PTT that corrects with mixing studies. Treatment is with infusion of factor VIII.

Hemophilia B (Christmas' Disease)

An X-linked recessive deficiency of factor IX deficiency. Patients present identically to hemophilia A. Correction occurs with normal plasma mixing, but

upon treatment with factor VIII, the patient shows no response. Treatment is with factor IX replacement.

Von Willebrand's Disease

Abnormal, low, or absent vWF. vWF exists as a multimer of proteins that form a complex with factor VIII. vWF is exposed when endothelial cells are damaged. vWF facilitates platelet adhesion to damaged endothelium. Patients present with spontaneous bleeding from mucous membranes and prolonged bleeding time with a normal platelet count.

HEMOGLOBINOPATHIES

Group of hereditary disorders characterized by the presence of structurally abnormal hemoglobin. Can be diagnosed with hemoglobin electrophoresis.

Sickle Cell Anemia

Caused by a mutation in the gene coding for the β-chain of hemoglobin. Results in RBCs assuming a sickle shape when deoxygenated, which then precipitate out of circulation and may occlude the microvasculature. Mutations in both β-chains defines sickle cell disease. A single affected chain is sickle cell trait.

- **Autosplenectomy:** Chronic obstruction of the spleen's blood supply causes recurrent infarcts leading to a shrunken and fibrotic spleen.
- **Pain crisis:** Occlusion of the microvasculature in the muscles causing pain.
- **Acute chest syndrome:** Occlusion of bone marrow can cause a fat embolus to the lungs, resulting in hypoxemia and possibly fatal cardiovascular collapse.
- ***Salmonella* osteomyelitis:** Increased susceptibility.

Thalassemia

A heterogeneous group of genetic disorders, transmitted in an autosomal codominant fashion, affecting the synthesis of hemoglobin. Characterized by a lack or decrease in synthesis of the α- or β-globin chains.

- **β-Thalassemia:** The β-chain of hemoglobin is absent or drastically reduced, resulting from a single base change mutation in the β-globin. **Target cells** are frequently seen on PBS.
  - **β-Thalassemia major:** Homozygous form of thalassemia associated with severe hemolytic anemia. Can produce skull deformities due to increased marrow hyperplasia.
  - **β-Thalassemia minor:** Heterozygous form of thalassemia, which may be asymptomatic or mildly symptomatic. Usually only a mild microcytic/hypochromic anemia.
- **α-Thalassemia:** Caused by deletions of one or more of the four α-globin genes.
  - **Silent carrier:** One gene is missing.
  - **Hemoglobin H:** Excess β-globin chains form stable tetramers.
  - **H Bart:** Excess δ-globin chains form stable tetramers.
  - **Fetal death:** All four are missing.

LYMPHOMA

Tumors typically present as painless masses within lymph nodes or other organs. Often result from proliferation of one cell with a specific marker, which allows differentiation based on antigen receptors. All lymphomas impair normal immunologic function. Patients may present with chronic infections or with symptoms due to the mass effect of the tumor.

Hodgkin's Lymphoma

Lymphoid neoplasm with characteristic Reed-Sternberg cells. Non-neoplastic inflammatory cells greatly outnumber neoplastic cells. Patients typically present with single, axial lymph node enlargement and the lymphoma spreads contiguously. There are four subtypes:

- **Nodular sclerosis:** Most common.
- **Mixed cellularity:** Most common in those aged >50 years.
- **Lymphocytic predominance:** Characteristic "popcorn cells."
- **Lymphocytic depletion:** Very rare.

Non-Hodgkin's Lymphoma

There are multiple types of NHL, differentiated from Hodgkin's lymphoma by the absence of Reed-Sternberg cells. Patients will often have multiple peripheral enlarged lymph nodes. Noncontiguous spread.

NON-HODGKIN'S LYMPHOMAS

Small Lymphocytic Lymphoma (SLL)/Chronic Lymphocytic Leukemia (CLL)

Similar tumors that differ only in the extent of peripheral blood involvement. Large numbers of circulating cells is called CLL, while those without large numbers are called SLL. Within lymph nodes there exist **proliferation centers** (foci of mitotically active prolymphocytes).

- **Smudge cells:** Neoplastic lymphocytes are fragile and frequently disrupted during smear preparation.
- **Hypogammaglobinemia:** Develops secondary to suppression of non-neoplastic B cells.
- **Autoimmune hemolytic anemia:** May develop as a result of the production of anti-RBC antigen Ig.

Follicular Lymphoma

Nodular or follicular pattern; these make up 40% of NHLs.

- **Association:** t(14;18) translocation.
- ***BCL2* gene:** BCL2 is an anti-apoptotic protein.

Mantle Cell Lymphoma

Resemble cells that reside in the mantle zone of lymph nodes. These make up 4% of NHLs. Frequent involvement of the GI tract causing lymphomatoid polyposis.

- **Association:** t(11;14) translocation leading to overexpression of **cyclin D1**.

Diffuse Large B-Cell Lymphoma

Aggressive tumors that respond well to chemotherapy. Linked to infection with EBV/HHV-8.

- **Association:** t(14;18) translocation.
- ***BCL2* gene.**

Burkitt's Lymphoma

Result from a *MYC* gene mutation resulting in overexpression. In Africa the tumors arise in the maxilla or mandible. In North America abdominal tumors are more common. Very aggressive growth pattern but amenable to chemotherapy.

- **Association:** EBV infection.
- **Histology:** "Starry sky" pattern.

ACUTE LEUKEMIAS

Proliferation of immature white blood cells. A block in differentiation leads to overproduction of premature cells with a prolonged generation time. There is accumulation of lymphoblasts in the blood and bone marrow. The major clinical consequences are suppression of RBCs, WBCs, and platelets (pancytopenia). Therapeutically, the aim is to suppress leukemic clonal expansion to allow the other blood cells to grow.

Acute Lymphoblastic Leukemia (ALL)

Occurs most commonly in children, representing one-third of all pediatric cancers. Patients present with petechiae, bleeding, frequent infections, fever, fatigue, and bone pain. Cure rates are high, now above 80% in complete remission. Blood smear reveals numerous lymphoblasts (pre-B or pre-T cells), typically from one stem cell progenitor. The lymphoblasts' nuclei are somewhat coarse with clumped chromatin and one or two nucleoli.

- **Philadelphia (Ph) chromosome:** Poor prognosis associated with translocations involving the *ML1* gene on chromosome **11q22** [**(t9;22)(q34;q11)**] (the Ph chromosome).
- **Association:** Down's syndrome.

Acute Myeloblastic Leukemia (AML)

More common in children, accounts for 20% of pediatric leukemias. Survival rates are about 50%. Patients present similarly to those with acute lymphocytic leukemia. Tumors are marked by a blockage in the differentiation of early myeloid cells. Immature myeloid cells (myeloblasts) accumulate in the marrow, replacing normal elements, and frequently circulate in the peripheral blood.

- **Auer rods:** Distinctive red-staining rod-like structures present in the promyelocytic variant.
- **AML M3 (acute promyelocytic leukemia):** Hypergranular promyelocytes, often with many **Auer rods** per cell, and may have reniform or bilobed nuclei. The presence of t(15;17)(q22;q12) translocation is characteristic, and this type responds well to **retinoic acid** therapy.

CHRONIC LEUKEMIAS

Proliferation of mature cells, with a more prolonged, less devastating course than the acute leukemias.

Chronic Lymphoblastic Leukemia (CLL)

More common in the elderly and presents with lymphadenopathy and hepatosplenomegaly. Stem cell progenitor produces large amounts of functionally incompetent lymphocytes. Patients present with all the signs and symptoms of decreased RBCs, platelets, and functional lymphocytes. Overexpression of bcl-2 leads to suppression of apoptosis.

- **Smudge cells:** Upon preparation of a PBS, CLL cells are fragile and prone to breaking during the preparation process, producing a characteristic smudge on the slide.

Chronic Myelogenous Leukemia (CML)

Increased myeloid stem cell proliferation. Can evolve into AML ("blast crisis"). Most patients present with splenomegaly and leukocytosis.

- **Associations:** Ph chromosome, t(9;22), and *bcr-abl* gene.
- **Blast crisis:** Similar to acute leukemia, patients have an overwhelming number of blast cells in circulation or within the bone marrow. May indicate the acquisition of new chromosomal abnormalities. Survival is short at this point.

OTHER LEUKEMIAS AND LYMPHOMAS

Extranodal Marginal Zone Lymphoma (MALT Lymphoma)

Low-grade B-cell tumors arising most commonly in Mucosal-Associated Lymphatic Tissue (salivary glands, small and large bowel, and lungs). May occur in the setting of *Helicobacter pylori* infection when treatment with antibiotics and eradication of the organism leads to tumor regression.

Hairy Cell Leukemia

Uncommon leukemia distinguished by the presence of leukemic cells that have fine, hair-like cytoplasmic projections. Cells express CD19/20 and surface Ig, as well as CD11c/103 (this is abnormal). The hairy cells can usually be seen in the PBS.

Mycosis Fungoides/Sézary Syndrome

Tumors of peripheral $CD4^+$ T cells characterized by involvement of the skin and therefore belonging to the group of **cutaneous** T-cell lymphomas.

- **Sézary syndrome:** Condition in which skin involvement is manifested clinically as a generalized exfoliative erythroderma along with an associated leukemia of Sézary cells. Results in a physical presentation termed **leonine facies.**

Adult T-Cell Leukemia/Lymphoma

T-cell neoplasm caused by infection with a retrovirus (human T-cell leukemia virus type 1 [HTLV-1]). Characterized by skin lesions, generalized lymphadenopathy, hepatosplenomegaly, hypercalcemia, and an elevated leukocyte count with multilobed CD4 lymphocytes. May cause progressive demyelinating disease of the CNS.

CHROMOSOMAL TRANSLOCATIONS

Many leukemias and lymphomas are characterized by a specific chromosomal translocation. Knowledge of the more common translocations can help yield a diagnosis (and answer test questions) (see Table 4-13).

PLASMA CELL DYSCRASIAS

Group of B-cell neoplasms caused by the expansion of a single clone of immunoglobulin-secreting cells. An increase in serum levels of a single homogeneous Ig or its fragments results.

Multiple Myeloma

Most common. Proliferation of plasma cells occurs within the bone marrow and produces characteristic **lytic lesions** of the skeletal system. Patients will often be anemic and have an elevated total protein on lab analysis.

- **Bence Jones proteins:** Seen in the urine. Renal failure is a serious complication.
- **Rouleau formation:** Agglutination of RBCs so that they resemble stacked poker chips on blood smear.

Monoclonal Gammopathy of Undetermined Significance (MGUS)

Elevated immunoglobulin levels without the significant clinical manifestations seen in multiple myeloma.

Heavy-Chain Disease

A disease in which only heavy chains are produced (usually of IgG, A, or M class).

Localized Plasmacytoma

Presence of a single lesion in the skeleton or soft tissues (extraosseous). The extraosseous lesions typically present in the upper respiratory tract.

TABLE 4-13. Common Chromosomal Translocations

Disease	Translocation
CML	t(9;22) Ph chromosome
Burkitt's lymphoma	t(8;14) c-myc
Follicular lymphoma	t(14;18) bcl-2
AML M3 type	t(15;17)
Ewing's sarcoma	t(11;22)
Mantle cell lymphoma	t(11;14)

LANGERHANS' CELL HISTIOCYTOSIS

Relatively rare conditions that are characterized by the clonal proliferation of Langerhans' cells (dendritic APCs normally distributed most prominently in the skin). Langerhans' cells have inclusion bodies (Birbeck's granules), which are often described as having a tennis racket–like appearance.

- **Letterer-Siwe disease:** Acute disseminated Langerhans' cell histiocytosis. Occurs before 2 years of age. Dominant clinical feature is the development of skin eruptions, secondary to infiltration of Langerhans' histiocytes.
- **Hand-Schüller-Christian disease:** Combination of calvarial bone defects, diabetes insipidus, and exophthalmos.
- **Vocal cord nodules:** Smooth hemispheric protrusions located on the true vocal cords. These occur chiefly in heavy smokers and singers.
- **Laryngeal papilloma:** A benign neoplasm on the true vocal cords, which forms a soft, raspberry-like excrescence, and is rarely more than 1 cm in diameter.
- **Juvenile laryngeal papillomas:** Usually singular in adults but multiple in children. Associated with human papillomavirus types 6–11.

Carcinoma of the Larynx

Accounts for 2% of all cancers. Presents in patients aged > 40 years, more often in men than in women. Associated with smoking and alcohol consumption and asbestos exposure. Manifests as persistent hoarseness.

- **Glottic tumors:** On the vocal cords, usually keratinizing.
- **Supraglottic tumors:** Above the vocal cords; one-third metastasize.
- **Subglottic tumors:** Below the vocal cords.

Nasopharyngeal Carcinoma

Strong link to EBV. EBV infects the host by replicating in the nasopharyngeal epithelium and then infecting nearby tonsillar B lymphocytes. High frequency in the Chinese.

NOTES

CHAPTER 5

Musculoskeletal and Connective Tissue

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MNEMONIC

There is only **1** shaft of the bone (diaphysis); **primary** ossification center is here.
There are **2** ends of the bone (epiphyses); **secondary** ossification centers are here.

KEY FACT

Achondroplasia is a disorder that affects endochondral ossification at the epiphyseal cartilage plates in long bones, resulting in premature closing of the epiphyses and short limbs.

KEY FACT

OI is often confused with child abuse, because exuberant healing of fractures creates callus. OI may also mimic osteosarcoma.

FLASH FORWARD

Rickets is a disease of children with vitamin D deficiency (and subsequently impaired calcium absorption) that affects the ossification of the epiphyseal cartilage plates. Softening, weakening, and bowing of the bones can occur.

Embryology

SKELETAL SYSTEM

Osteogenesis

Development

Bone develops from two sources: Mesenchyme (intramembranous ossification) and cartilage (endochondral ossification).

- **Intramembranous ossification:** Flat bones, such as those that make up the skull, develop directly from mesenchyme in preexisting membranes.
- **Endochondral ossification:** Most bones, including long bones in the appendicular skeleton, develop from mesenchyme that has condensed into cartilage first. The **primary center of ossification** in the cartilaginous model forms the shaft of the bone (diaphysis). The ends of the bone (epiphyses) remain cartilaginous for several years after birth, during which the **secondary centers of ossification** appear. Bone lengthening occurs in the epiphyseal cartilage plate at the diaphysial-epiphyseal junction until it ossifies by about 20 years of age (see Figure 5-1).

Congenital Malformations

- **Osteogenesis imperfecta (OI):** Caused by a deficiency in **type I collagen**, usually due to an autosomal dominant gene defect affecting collagen synthesis. Characterized by extremely fragile bones often resulting in fractures while still in utero. Also characterized by blue sclerae (thinning of sclerae overlying the choroidal veins leads to their subsequent reflection), poor wound healing, and hearing loss (in about 50%).
- **Achondroplasia:** Also known as achondrodysplasia, it is the most prevalent form of dwarfism. **Autosomal dominant** disorder caused by a mutation in the gene for a fibroblast growth factor (**FGF-3**) receptor on **chromosome 4p.** Constitutive activation of this receptor leads to inhibition of chondrocyte proliferation. Endochondral ossification is impaired, as the epiphyseal growth plate becomes small and disorganized, preventing proper bone

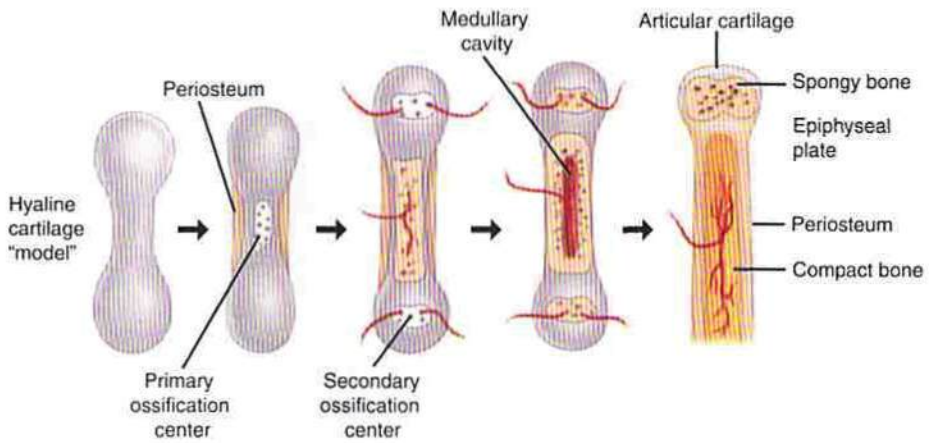


FIGURE 5-1. Bone growth. Primary ossification center in the diaphysis; secondary ossification center in the epiphyses.

growth. This leads to disproportionately short arms and legs, and often disproportionately large head and trunk. In some cases, severe spinal deformity may compress the spinal cord. Homozygotes experience more severe disease that may result in neonatal death. Risk factors include increasing paternal age.

- **Marfan's syndrome:** An **autosomal dominant** mutation in the gene for the protein **fibrillin** (the fibrillin-1 gene is located on chromosome 15q21.1) causes abnormal elastin fibers that affect the skeletal, cardiac, and ocular systems. Skeletal changes include tall stature, long limbs, hyperextendable joints, long and tapering digits, pectus excavatum, and scoliosis (see Figure 5-2).
- **Gigantism and acromegaly: Hyperpituitarism** causes excessive amounts of GH that can result in gigantism in infants (increased height and excessive body proportions) and acromegaly in adults (increased bone growth in the jaw, hands, and feet, as well as increased soft tissue and visceral organ growth). IGF-1 levels are usually elevated secondary to excess GH; this is often seen in adolescence (secondary) to pubery, as well as in pathologic conditions. Further diagnostics include the **oral glucose tolerance test (OGTT)**: GH level should decrease after an oral glucose load; if not, it is diagnostic of pituitary GH excess.
- **Cretinism:** Caused by a **deficiency in fetal thyroid hormone** through any of the following etiologies: Lack of dietary iodine (especially in areas where there is little iodine in the soil and water); mutations in thyroid hormone synthesis; and agenesis of the thyroid gland. Characterized by mental retardation, short stature, **impaired bone growth,** and neurologic disorders of muscle tone and coordination.



FIGURE 5-2. Marfan's syndrome. Note bony changes, long limbs, and long, tapering digits. (Courtesy of the Hall family.)

KEY FACT

Laron's syndrome is another form of dwarfism. It is an **autosomal recessive** disorder in which a **defect in the growth hormone receptor (GHR)** causes a lack of responsiveness to increased levels of GH in the body.

FLASH FORWARD

Ocular findings in Marfan's syndrome include **ectopia lentis** (lens dislocation) in 50% of patients. Dislocation is usually *upward and toward the temples.* This is in contrast to ectopia lentis in homocystinuria, which is usually downward and into the anterior chamber.

FLASH FORWARD

Marfan's syndrome is associated with ascending aortic dissection, mitral valve prolapse, and cerebral berry aneurysms. These are covered in the cardiovascular chapter.

FLASH FORWARD

Cretinism is intimately related to thyroid hormone synthesis and hypothyroidism.

FLASH BACK

The pharyngeal arches, pouches, grooves, and membranes form much of the head and neck, including arches 4 and 6 that provide part of the structure of the viscerocranium: the laryngeal cartilage. These pharyngeal structures and their derivatives are covered in the general embryology section.

KEY FACT

The frontal suture usually disappears by age 6 years. If it remains after this age, it may be called a "metopic suture" and can be confused with a fracture to the untrained eye.

Skull

Development

Mesenchyme around the fetal brain develops into the skull, which can be divided into two parts:

- Neurocranium: Includes the flat bones and base of the skull.
- Viscerocranium: Includes the bones of the face and laryngeal cartilage.

Most of the bones in the neurocranium and viscerocranium are derived from **neural crest cells,** though there are some exceptions (the base of the occipital bone comes from the mesoderm of the occipital sclerotomes, and the laryngeal cartilage is derived from the pharyngeal arches 4 and 6).

The flat bones in the skull are separated by five connective tissue **sutures** which allow expansion of the skull while the brain grows:

- Frontal suture.
- Sagittal suture.
- Lambdoid suture.
- Coronal suture.
- Squamosal suture.

Fontanelles are areas between the flat bones of the skull where the sutures meet. As the surrounding bones grow, all fontanelles usually close by about 2 years of age. Fontanelles allow room for the brain to finish growing. There are six fontanelles (see Figure 5-3):

- Anterior fontanelle: Closes by the end of the second year.
- Posterior fontanelle: Closes within 2–3 months.
- Sphenoid fontanelle (2): Close within 2–3 months.
- Mastoid fontanelles (2): Close by the end of the first year.

Congenital Malformations

- **Microcephaly:** Failure of the brain, and subsequently the skull, to grow. Affected children are severely mentally retarded. The etiology may be an autosomal recessive genetic mutation or in-utero infection.

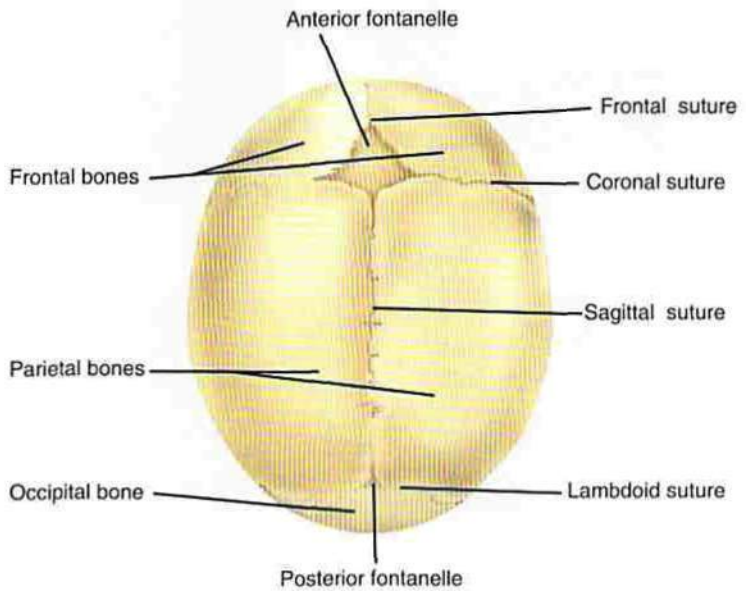


FIGURE 5-3. Normal skull of a newborn with sutures and fontanelles.

- **Craniosynostoses:** Premature closure of the sutures may lead to abnormal shapes of the skull:
  - Oxycephaly: Early closure of the lambdoid and coronal sutures can lead to a cone-shaped skull. This is the most severe form.
  - Plagiocephaly: Unilateral closure of the lambdoid and coronal sutures, leading to an asymmetric skull.
  - Scaphocephaly: Premature closure of the sagittal suture leads to an elongated skull in the anterior-posterior direction. It is the most common form.

Vertebral Column

Development

At week 4 of embryonic development, the mesenchymal cells from the sclerotomes of the somites begin to surround the notochord, the neural tube, and the body wall. In each of these three areas, significant structures of the vertebral column are formed.

- Around the **notochord:** Each sclerotome consists of a layer of loosely arranged cells cranially and a layer of densely arranged cells caudally. Some of the densely arranged cells move cranially and form the **intervertebral disk.** The rest of the dense cells combine with the loosely arranged cells to form the **centrum.** The centrum forms the body of the vertebra. The notochord degenerates where it is surrounded by the developing vertebral bodies. Between the vertebral bodies, the notochord develops into the **nucleus pulposus** of the intervertebral disk (see Figure 5-4).
- Around the **neural tube:** Mesenchymal cells form the vertebral arch.
- In the **body wall:** Mesenchymal cells from the costal processes that then go on to form the ribs (see the section on rib development below).

During week 6 of embryonic development, the mesenchymal vertebra goes through chondrification to create a cartilaginous vertebra. Two **chondrification centers** appear in the centrum to form a cartilaginous body. Chondri-

FLASH BACK

In embryonic development, the neural tube becomes the spinal cord, and the notochord eventually forms the vertebrae.

FLASH BACK

The development of the vertebral column is likely regulated by paired box genes (transcription factors specific for a certain tissue type), and homeobox genes (genes that have "homeobox" sequences that contain transcription factors involved in the development of an organism; "Hox" genes are a subset of these involved in development of the body axis).

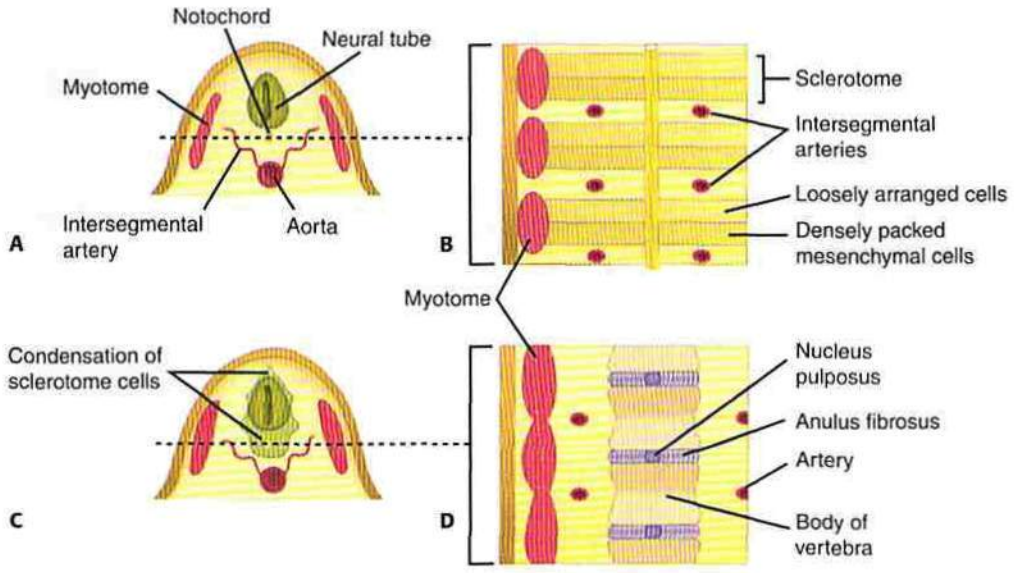


FIGURE 5-4. Early vertebral column development. (A) and (B) show transverse and frontal sections of a 4-week-old embryo, respectively. (C) and (D) show the same sections in a 5-week-old embryo. Note the condensation of sclerotome cells around the neural tube and notochord by week 5. Also note how the loosely arranged cells and densely arranged cells form the body of the vertebra and how the notochord becomes the nucleus pulposus in between the vertebral bodies.

fication centers in the vertebral arch (originally from the neural tube) fuse with the centrum and each other, giving rise to the spinous and transverse processes.

By the end of developmental week 8, three **primary ossification centers** appear: One in the centrum and two in the vertebral arch (one on each side). These three bony parts are connected by cartilage at the time of birth; they fuse together completely by the age of 3–6 years. After puberty, **secondary ossification centers** appear at the tips of the spinous and transverse processes as well as the rims of the vertebral body (the **annular epiphyses**). These centers eventually fuse completely by the age of 25 years.

KEY FACT

The notochord is the embryological origin of the nucleus pulposus.

The following vertebrae do not ossify in the above manner:

- Atlas (C1): Has no vertebral body.
- Axis (C2): Has a **dens** (odontoid process) that is the developmental remnant of the body of the atlas.
- Sacrum: These five vertebrae fuse together to form a wall of the pelvic cavity.
- Coccyx: Four rudimentary vertebrae fuse into a small triangle at the base of the spine.

KEY FACT

The anulus fibrosis is made of type III cartilage.

The four main spinal areas are associated with four specific curvatures, two of which are primary (form during fetal development), and two of which are secondary (develop after birth).

- Cervical: Secondary; forms as the infant lifts its head.
- Thoracic: Primary.
- Lumbar: Secondary; forms after the child begins to walk.
- Sacral: Primary.

Congenital Malformations

- **Chordoma:** This is a remnant of the notochord. One-third of chordomas become slowly growing, malignant tumors that infiltrate surrounding tissues including the bone, and usually form at the base of the skull growing into the nasopharynx. Chordomas can occur anywhere along the spine, with many occurring in the lumbosacral and sacrococcygeal areas as well. Depending on the location, patients can present with diplopia and headache (if near the skull), or lower back and leg pain (if in the lumbosacral spine). The prognosis is poor, with only half of patients surviving past 5 years.
- **Variations in the number of vertebrae:** The vast majority of people have a total of 33 vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 fused in the coccyx. Less commonly, people either have one vertebra too many or one too few. It is extremely rare for variations to occur in the cervical region.
- **Klippel-Feil syndrome (brevicollis):** A syndrome with the following constellation of symptoms:
  - Short neck.
  - Decreased range of motion in the cervical spine.
  - Low hairline.
  - It is caused by fusion of the cervical vertebrae, though the etiology is unclear. Defects in the thoracic and lumbar spine causing **scoliosis** are common in this disorder. Renal anomalies and hearing loss are also common.

Spina Bifida

This spinal defect occurs when the two halves of the vertebral arch fail to fuse, most commonly in the lumbosacral region (L5 and/or S1). Because of the defect, the vertebral arch consists of two parts, and is hence "bifid." There are many variations of spina bifida, ranging from mild to severe, depending on to what degree the spinal cord and/or meninges protrude through the defect (see Figure 5-5).

- **Spina bifida occulta:** This is the mildest version, occurring in 10%–25% of the population. The spinal cord and nerves are usually normal, and there are no clinical symptoms other than a small tuft of hair that may grow in the lumbosacral region of the back.
- **Spina bifida with meningocele:** A type of "spina bifida cystica" in which a sac containing meninges and cerebrospinal fluid protrudes through the vertebral defect. The spinal cord is not affected.
- **Spina bifida with meningomyelocele:** A more severe type of "spina bifida cystica" in which the sac protruding through the vertebral defect contains not only meninges and CSF, but the spinal cord and/or nerve roots as well. The patient is more likely to have neurologic symptoms with this disorder. Patients are also more likely to have latex allergies, Arnold-Chiari malformations, and syringomyelia.
- **Spina bifida with rachischisis:** The most severe type of "spina bifida cystica" in which there is an open neural tube due to the failure of the posterior neuropore to close at the end of week 4 of embryonic development. This results in the spinal cord actually protruding through the vertebral defect all the way to the skin, being exposed to the outside of the body. Often fatal.

FLASH BACK

When a similar bony defect occurs at the base of the skull, a meningocele (protrusion of the meninges and CSF), meningoencephalocele (protrusion of the meninges and brain), or meningohydroencephalocele (protrusion of meninges, brain, and ventricle) may occur.

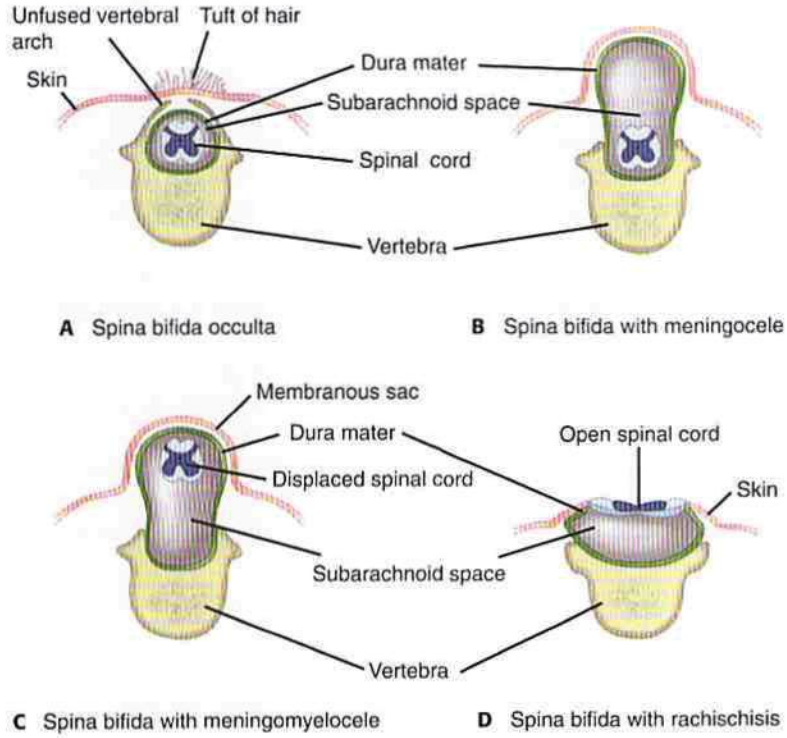


FIGURE 5-5. Spina bifida. Note the range of spina bifida types, depending on what protrudes through the vertebral arch defect. (A) Spina bifida occulta. (B-D) These defects are all under the umbrella term of "spina bifida cystica" because of their cyst-like sac protrusion.

KEY FACT

The "triple screen" is a blood test that measures AFP, β-human chorionic gonadotropin, and unconjugated estriol. It is done at weeks 16–18 of pregnancy to estimate the risk of a fetus having certain birth defects or health problems. A high level of **AFP** should lead one to consider **spina bifida,** though it may also be seen in other congenital disorders such as anencephaly. In contrast, Down's syndrome may cause a "down" (low) AFP level.

The maternal serum level of α-fetoprotein (AFP) is high in spina bifida. Further evaluation using ultrasound can be done during the first trimester.

Causes of neural tube defects such as spina bifida cystica include genetic factors, increased alcohol intake during pregnancy, and certain drugs taken during the first trimester, most notably valproic acid, an anticonvulsant. All pregnant women should take folic acid supplements to help prevent neural tube defects.

Hemivertebra

This malformation occurs when one of the two chondrification centers in the centrum fails to appear. Only half of the vertebral body is then able to form. This produces a lateral curvature and rotation of the spine known as **scoliosis.**

Spondylolisthesis

This defect occurs when the vertebral arch pedicles fail to fuse with the vertebral body, allowing the vertebral body to be displaced anteriorly, causing an anterior curvature of the spine known as **lordosis.**

KEY FACT

When testing a patient for thoracic outlet syndrome, look for **Adson's sign:** Have the patient maximally extend the neck and rotate the head toward the side being tested. Look for a decrease in the ipsilateral radial pulse and listen for a subclavian bruit.

Ribs

Development

Mesenchymal cells from the sclerotomes of the somites that surround the body wall form the costal processes that develop into ribs. Though costal processes occur at all vertebrae, only the thoracic vertebrae develop ribs. The "true ribs" are the first seven that attach to the sternum. The "false ribs," ribs 8–12, attach to the sternum via other ribs. The last two ribs are "floating ribs" that do not attach to the sternum at all.

Congenital Malformations

- **Accessory ribs:** An extra rib can develop from the costal processes of a cervical or lumbar vertebral body. Though a lumbar rib is more common, a cervical rib arising from C7 can cause **thoracic outlet syndrome.** In this syndrome, the extra cervical rib can compress the neurovascular bundle at the thoracic outlet.
  - The lower nerve roots of the brachial plexus (C8 and T1) are affected most commonly, leading to neurologic symptoms such as pain and tingling in the ulnar nerve distribution.
  - The upper nerve roots (C5, C6, and C7) can also be compressed, causing similar symptoms in the radial nerve distribution as well as the neck, ear, and torso.
  - A compressed subclavian vein can lead to swelling and cyanosis in the upper extremity of the affected side, and a compressed subclavian artery can cause pallor, pulselessness, low-BP, coolness, and rare small infarcts in the affected upper extremity.

FLASH BACK

The **interscalene triangle** is bordered anteriorly by anterior scalene, posteriorly by middle scalene, and inferiorly by medial surface of the first rib. An accessory cervical rib can compress this small area causing thoracic outlet syndrome.

FLASH FORWARD

The brachial plexus is compressed in **thoracic outlet syndrome.** Check the neurology chapter for the peripheral nerves that stem from the plexus to understand the anatomic distribution of symptoms.

Limbs

Development

Development of the limb bones begins when the early limb buds form at about the fourth week of embryonic development. By the fifth week, mesodermal cells from the lateral plate migrate into the limb buds. Structures at the base and outer edge of the limb buds are important to know.

- A thickened region of ectoderm called the **apical ectodermal ridge (AER)** develops at the edge of the limb bud and produces **FGF** that induces the mesodermal cells to grow outward and form cartilage.

- The **zone of polarizing activity** at the base of the limb bud produces the **sonic hedgehog** protein which activates **homeobox-containing (*Hox*) genes** that direct the patterned organization of the limbs and digits.

The rest of limb development follows this general timeline:

- Week 6: Digital rays develop in the hands and feet, and digit formation involves selective **apoptosis** within the AER. By the end of week 6, the cartilaginous models of the limb bones are complete.
- Weeks 7–12: The long bones undergo endochondral ossification as discussed previously, and most of the primary ossification centers develop.
- Before birth: Several secondary ossification centers develop, though many develop after birth as well.
- Adult age: The primary ossification in the diaphysis does not fuse with the secondary ossification in the epiphysis until adult age, allowing for complete bone growth. At this time, the epiphyseal plate between the two finally ossifies, and bone growth ends.

Congenital Malformations

Limb anomalies range from problems affecting limb bud development causing complete absence of limbs, to problems in the growth or differentiation of limbs, causing shortened or deformed extremities. The anomalies listed below may be caused by genetic factors, environmental factors, or both.

- **Amelia:** Complete absence of one or more limbs, often due to maternal ingestion of a teratogen, such as **thalidomide.**
- **Meromelia:** Partial absence of one or more limbs.
- **Cleft hand and foot:** Also known as "lobster-claw deformities." Several of the digital rays fail to develop centrally; the lateral digits fuse, causing a claw-shaped hand or foot.
- **Congenital clubfoot:** A common anomaly occurring about once in every 1000 births, involving any deformity in the ankle bone (talus) of the foot. The most common type of clubfoot is **talipes equinovarus,** in which the foot is inverted and turned in medially. A genetic predisposition seems to be involved. The majority of cases involve abnormal positioning of the feet in the uterus.
- **Anomalies of the digits:**
  - **Polydactyly:** An autosomal dominant trait that causes extra fingers or toes to develop, usually medially or laterally. More common in African Americans. In Caucasians, polydactyly is associated with heart disorders.
  - **Syndactyly:** This is the most common limb anomaly and may be either autosomal recessive or autosomal dominant. Cutaneous syndactyly involves simple webbing of the digits, usually in the toes. A more severe form is osseous syndactyly in which the bones of the digits fuse (as in the lateral digits in clubfoot) when the divisions between the digital rays fail to develop.
  - **Brachydactyly:** Hypoplasia of the fingers or toes. It is uncommon, often inherited as an autosomal dominant trait, and usually associated with short stature.
- **Holt-Oram syndrome:** Also known as **heart-hand syndrome.** Due to mutations in the ***TBX5*** gene on chromosome 12, a factor important in both cardiac and upper limb development. The main manifestations of this disorder commonly include **atrial septal defects** and **abnormalities of the thumbs.** Other cardiac abnormalities include ventral septal defects, atrioventricular block, and atrial fibrillation.

KEY FACT

The cartilage of the upper limbs develop before that of the lower limbs. The clavicle is the first bone to undergo primary ossification; however, this is closely followed by the femurs. The first secondary ossification site is in the knees.

FLASH BACK

Many trisomy syndromes are associated with limb defects.

- Trisomy 21 (Down's syndrome): **Clinodactyly** (curving of the fingers).
- Trisomy 18 (Edwards' syndrome): Flexed digits and "rocker-bottom" feet.
- Trisomy 13 (Patau's syndrome): **Polydactyly.**
- Defects in chromosome 12 can cause **Holt-Oram syndrome,** described in this section.

KEY FACT

The critical window of limb development occurs during the third to fifth week. Teratogens ingested early in this window may cause severe defects. In the late 1950s and early 1960s, many mothers took **thalidomide,** a sedative and antiemetic which caused severe teratogenic limb defects including amelia.

FLASH BACK

Today the only FDA-approved use for thalidomide is pain relief from erythema nodosum leprosum, the skin manifestation of leprosy.

- **Congenital hip dislocation:** A very common disorder, affecting about one in every 1000 infants. Predisposing factors include female gender, Native American heritage, first-born status, and breech birth. Diagnosed by physical exam:
  - Positive Ortolani's test: One hears a low-pitched click when abducting the hip.
  - Positive Barlow's maneuver: While keeping hips in the adducted position, one hears a click when applying gentle pressure posteriorly.
  - Positive Galeazzi's sign: One leg appears longer than the other. This may be more reliable for diagnosis in older infants.

Treatment includes a Pavlik's harness, then open or closed reduction, depending on the age and severity of disease.

MUSCULAR SYSTEM

Almost all muscles in the human body develop from mesoderm (the notable exceptions being the dilator pupillae and sphincter of the iris that develop from the neuroectoderm). Cardiac and smooth muscles develop from **splanchnic mesoderm,** whereas most skeletal muscles develop from regions of the somites called **myotomes.** Developmental anomalies can lead to the absence of or variation in muscles, which are generally benign.

KEY FACT

The dilator pupillae and sphincter muscles of the iris originate from neuroectoderm, not mesoderm.

Skeletal Muscle

Mesenchymal cells in the myotome areas of the somites differentiate into **myoblasts** that then elongate and fuse into tubular structures called **myotubes**. Fibroblasts and the external laminae that form around the muscle tubules encase the muscle in a fibrous sheath during its development. Myofilaments, myofibrils, and other muscle-specific organelles develop early. Skeletal muscle starts to grow as myotubes fuse together; after the first year, the increase in myofilaments leads to muscle growth.

Different myotomes give rise to different muscles in the body, generally depending on location.

Muscular Development of the Head and Neck

- **Preoptic myotomes** give rise to extraocular muscles.
- **Occipital myotomes** give rise to the tongue muscles.

Muscular Development of the Trunk

Each myotome of each somite in the trunk region divides into two parts: An **epaxial division** on the dorsal side and a **hypaxial division** on the ventral side. Each developing spinal nerve splits to innervate both areas: a **dorsal primary ramus** to the former and a **ventral primary ramus** to the latter.

- **Epaxial myotomes** develop into intrinsic back muscles and extensor muscles of the neck and vertebrae.
- **Hypaxial myotomes** develop into limb, abdominal, and intercostal muscles, as well as the following based on location:
  - Cervical myotomes form the prevertebral, geniohyoid, infrahyoid, and scalene muscles.
  - Thoracic myotomes form the flexor muscles of the vertebrae.
  - Lumbar myotomes form the quadratus lumborum muscle.
  - Sacrococcygeal myotomes form pelvic diaphragm muscles.

Muscular Development of the Limbs

Mesenchyme from the myotomes in the limb buds condense into two areas: posterior and anterior condensations.

The **posterior condensations** form:

- Extensor and supinator muscles in the upper limbs.
- Extensor and abductor muscles in the lower limbs.

The **anterior condensations** form:

- Flexor and pronator muscles in the upper limbs.
- Flexor and adductor muscles in the lower limbs.

Development of the Diaphragm

The diaphragm arises from several different parts of the developing body cavity and functions to separate the abdominal cavity from the thoracic cavity. The embryonic components making up the diaphragm include:

- Septum transversum.
- Pleuroperitoneal folds.
- Body wall.
- Dorsal mesentery of the esophagus.

MNEMONIC

Several **P**arts **B**uild **D**iaphragm:

Septum transversum
Pleuroperitoneal folds
Body wall
Dorsal mesentery of esophagus

At around week 3 of embryonic development, the **septum transversum** develops from the ventral aspect of the body wall, growing dorsally to separate the heart from the liver. It forms the primordium of the **central tendon of the diaphragm**, which is innervated by the phrenic nerves. The septum transversum eventually fuses with the **pleuroperitoneal membranes** and **esophageal mesentery** to complete the primordial diaphragm. The pleuroperitoneal membranes initially make up a large dorsal portion of the primordial diaphragm, but contribute very little to the infant's diaphragm. The esophageal mesentery forms the median portion and **crura of the diaphragm.**

Later in embryonic development, between weeks 9 and 12, the internal muscular layer of the lateral body wall fuses with the primordial diaphragm, contributing to its periphery and then forming the costodiaphragmatic recesses (see Figure 5-6).

Smooth Muscle

Splanchnic mesenchyme around the primordial gut endoderm develops into the smooth muscle in the GI tract. Somatic mesoderm gives rise to the smooth muscle in the walls of blood and lymphatic vessels.

Cardiac Muscle

Mesenchyme around the heart tube migrates from the lateral splanchnic mesoderm and then develops into cardiac myoblasts. Unlike skeletal muscle, cardiac muscle fibers do not fuse together, but rather differentiate and grow as single cells. By week 4 of development, heart muscle can be recognized in the embryo.

FLASH BACK

Heart muscle (and CNS) can be recognized in the embryo by 4 weeks of gestation.

Congenital Malformations

Congenital diaphragmatic hernia. Also known as hiatal hernia, this condition occurs with incomplete development of the diaphragm, usually a posterolateral defect on the left. Because the abdominal contents herniate into the thorax, the lungs are not able to expand fully, thus resulting in pulmonary

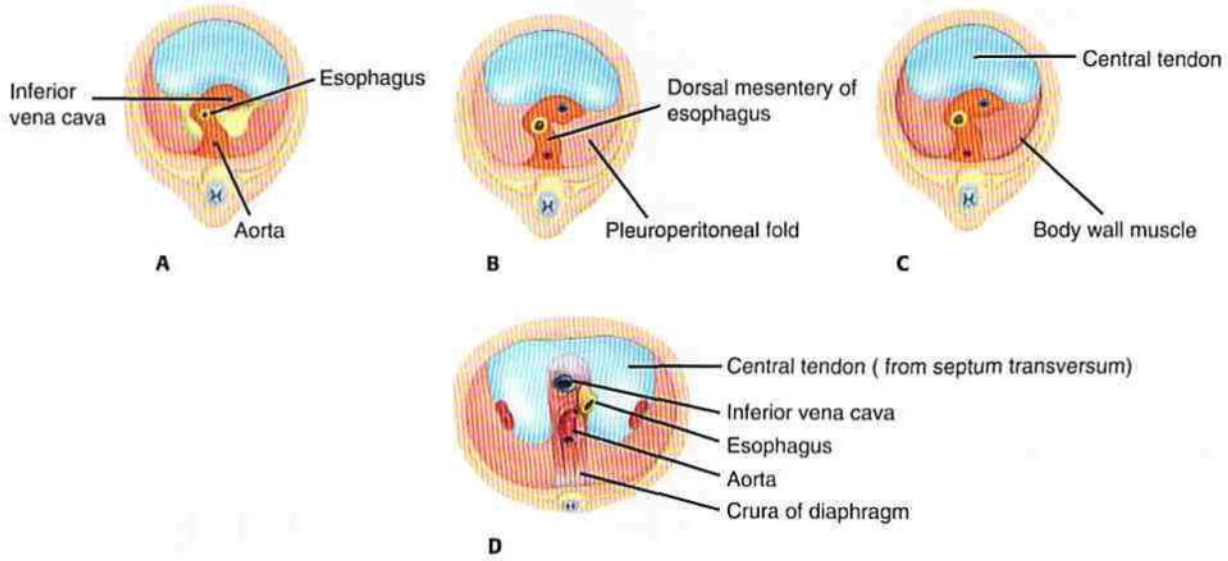


FIGURE 5-6. Development of the diaphragm. The different components making up the diaphragm in an embryo at 5 weeks (A), 6 weeks (B), and 12 weeks (C). The diaphragm of an infant (D). Please note that though the pleuroperitoneal membrane makes up much of the posterior aspect of the diaphragm in the embryo, the muscular ingrowth from the body wall takes over much of that region by the time the infant is born.

hypoplasia, and in rare severe cases, pneumothorax. Polyhydramnios is often associated with congenital diaphragmatic hernia. Prenatal diagnosis requires MRI or ultrasound evidence of abdominal organs displaced into the thorax.

PRUNE BELLY SYNDROME. This syndrome occurs when **abdominal musculature** is severely underdeveloped or even absent, most likely due to the involvement of myoblasts in the hypaxial myotomes. **Urinary tract defects** are commonly associated, including tortuous and dilated ureters, prostatic hypoplasia, and a thick-walled bladder. Cryptorchidism is extremely common. Pulmonary hypoplasia is also seen due to the pressure of the abdominal contents on the thorax. Diagnosis is made with neonatal ultrasound, and treatment includes surgical repair for severe cases.

POLAND'S SYNDROME. This uncommon anomaly occurs when the **pectoralis major** muscle is completely or partially absent. Often, just the sternal head of the pectoralis major is absent. There may also be partial absence of the ribs and sternum, mammary gland aplasia, nipple hypoplasia, and absence of the serratus anterior and latissimus dorsi muscles. This syndrome usually causes no disability, as the shoulder muscles are able to compensate for the missing muscle.

CONGENITAL TORTICOLLIS. This occurs when the **sternocleidomastoid (SCM)** muscle is either injured at birth or congenitally shortened such that the infant's head is rotated and tilted in a fixed position. Contraction of one SCM tilts the head ipsilaterally, but due to the attachment of the SCM to the mastoid process posterior to the fulcrum of the head, **rotation is in the contralateral direction.** So, if the head is turned **right**, the **left** SCM is involved.

ACCESSORY MUSCLES. Generally benign, accessory muscles can occur virtually anywhere in the body. One of the more common and occasionally clinically significant cases includes that of an **accessory soleus muscle**, which is believed to affect about 6% of the population. In embryonic development, the soleus muscle may split to form an accessory muscle. Occasionally, this development can cause pain in the posteromedial area of the ankle after strenuous exercise.

Anatomy

SKELETAL SYSTEM

Two types of connective tissue make up the skeletal system: bone and cartilage. All bones are made up of an outer layer of **compact** bone and an inner mass of **spongy** bone (mainly replaced by a **medullary cavity**) with different bones having different relative amounts of each. Compact bone is primarily for weight bearing, while the medullary cavity and areas around the spongy bone spicules house the formation of blood cells and platelets (see Figure 5-7). Cartilage forms in the areas of the skeletal system where movement is required. Unlike bone, cartilage does not have its own blood supply and receives nutrition via diffusion.

There are two main divisions of the skeletal system: the **axial skeleton** (skull, vertebrae, hyoid bone, ribs, and sternum) and the **appendicular skeleton** (limb bones, shoulders, and pelvic girdles).

Major Bones

SKULL

The bones of the skull can be divided into two main groups: The **neurocranium** and **viscerocranium.**

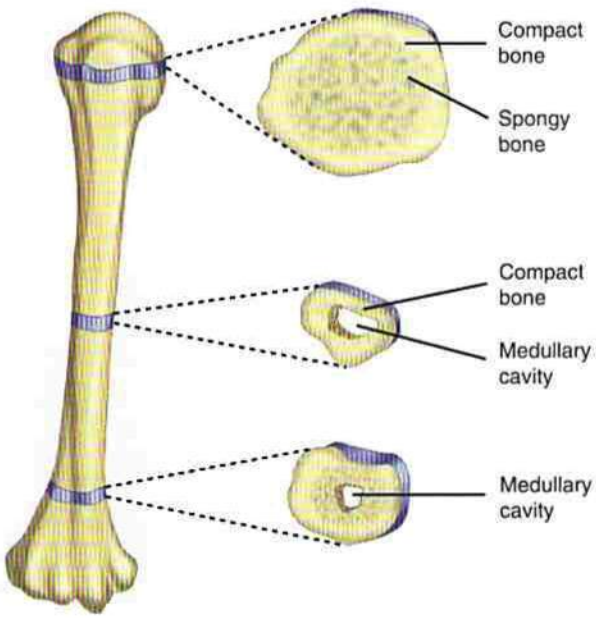


FIGURE 5-7. Humerus with transverse sections. Compact bone, spongy bone, and the medullary cavity are shown.

FLASH FORWARD

The **pterion** is the area where four of the bones of the neurocranium meet: frontal, parietal, temporal, and sphenoid. It is at this structurally weak point where the **middle meningeal artery** is easily ruptured in the event of trauma to the side of the head, causing an epidural hematoma.

MNEMONIC

Structures passing through the superior orbital fissures: **L**azy **F**rench **T**arts **S**it **N**aked **I**n **A**nticipation **O**f **S**ex.

Lacrimal nerve (branch of the ophthalmic nerve, CN V_1)
Frontal nerve (branch of the ophthalmic nerve, CN V_1)
Trochlear nerve (CN IV)
Superior division of the oculomotor nerve (CN III)
Nasociliary (branch of the ophthalmic nerve, CN V_1)
Inferior division of the oculomotor nerve (CN III)
Abducens nerve (CN VI)
Ophthalmic vein
Sympathetic fibers

The **neurocranium** houses the brain and associated blood vessels, cranial nerves, and meninges. It consists of eight mostly flat bones that are connected by sutures:

- Frontal bone.
- Parietal bones (2).
- Temporal bones (2).
- Occipital bone.
- Sphenoid bone.
- Ethmoid bone (along with parts of the temporal and occipital bones, makes up the base of the skull).

The major **sutures** connecting the bones of the neurocranium are as follows:

- Coronal suture: Connects the frontal bone with the parietal bones.
- Sagittal suture: Connects the two parietal bones.
- Squamosal sutures: Connect the temporal bones with the parietal bones.
- Lambdoid suture: Connects the occipital bone with the parietal and temporal bones.

The **viscerocranium**, as the name implies, makes up the "face" of the skull—namely, the orbits, nasal cavities, and jaw. It consists of 14 bones (see Figure 5-8):

- Nasal bones (2).
- Lacrimal bones (2).
- Zygomatic bones (2).
- Vomer.
- Palatine bones (2).
- Inferior nasal conchae (2).
- Maxillae (2).
- Mandible.

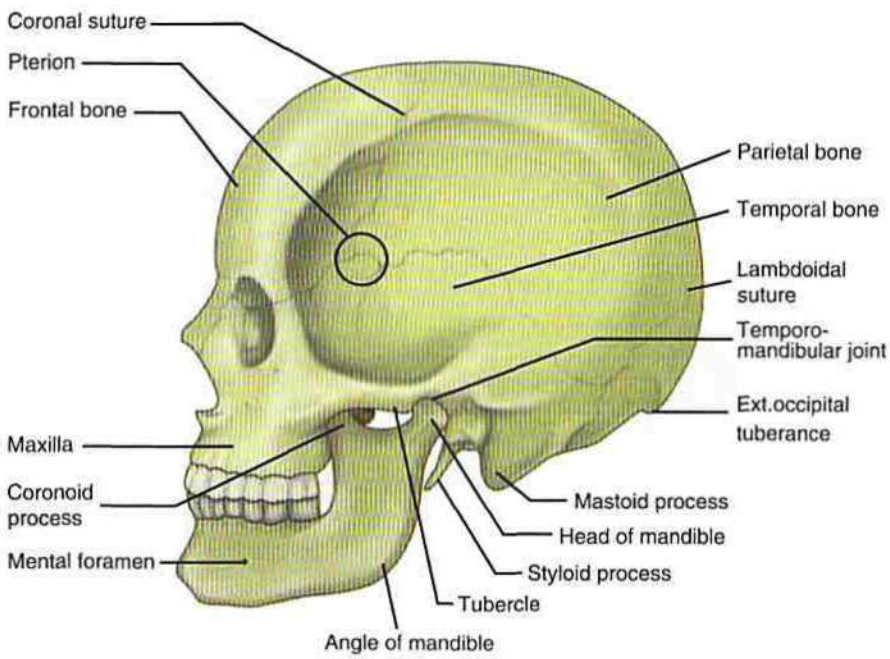


FIGURE 5-8. Lateral view of the skull. (Modified, with permission, from White JS, *USMLE: Road Map: Gross Anatomy*, 2nd ed, New York: McGraw-Hill, 2006: 188.)

The inner surface of the cranial base contains three depressions: the **anterior fossa, middle fossa,** and **posterior fossa.** Through each fossa various nerves and blood vessels are transmitted through holes in the skull called **foramina.** Knowing the structures associated with each foramina is extremely high-yield for Step 1 (see Table 5-1).

MNEMONIC

Structures passing through the foramen ovale: **MALE**

Mandibular nerve (CN V_3)
Accessory meningeal artery
Lesser petrosal nerve
Emissary veins

Vertebral Column

The vertebral column is made up of 33 vertebrae (see Figure 5-9). A typical vertebra has a **vertebral body** anteriorly (to support body weight), a **vertebral**

TABLE 5-1. Structures Transmitted Through Skull Foramina

Foramen	Bone	Fossa	Transmitted Structure(s)
Cribriform plate foramina	Ethmoid	Anterior	Olfactory nerve (CN I).
Optic canals	Sphenoid (lesser wing)	Middle	Optic nerves (CN II). *Ophthalmic arteries.*
Superior orbital fissures	Between the lesser and greater wings of the sphenoid	Middle	Ophthalmic veins. CN III. CN IV. CN V_1 (*ophthalmic*). CN VI. Sympathetic fibers.
Carotid canal	Between temporal (petrous *portion) and sphenoid (greater* wing)	Middle	Internal carotid artery.
Foramen rotundum	Sphenoid (greater wing)	Middle	CN V_2 (Maxillary).
Foramen ovale	Sphenoid (greater wing)	Middle	CN V_3 (mandibular). Accessory meningeal artery. Lesser petrosal nerve. Emissary veins.
Foramen spinosum	Sphenoid (greater wing)	Middle	Middle meningeal artery and vein.
Foramen lacerum	Between temporal (petrous portion) and sphenoid	Middle	Nothing transmits through, but the internal carotid artery passes across it.
Internal acoustic meatus	Temporal (petrous part)	Posterior	CNs VII and VIII.
Jugular foramen	Between temporal (petrous portion) and occipital	Posterior	CNs IX, X, and XI, internal jugular vein, sigmoid sinus.
Hypoglossal canal	Occipital	Posterior	CN XII.
Foramen magnum	Occipital	Posterior	Spinal roots of CN XI, vertebral arteries, anterior and posterior spinal arteries, dural veins, medulla, meninges.
Mastoid foramen	Temporal (petrous)	Posterior	Mastoid emissary vein from the sigmoid sinus.

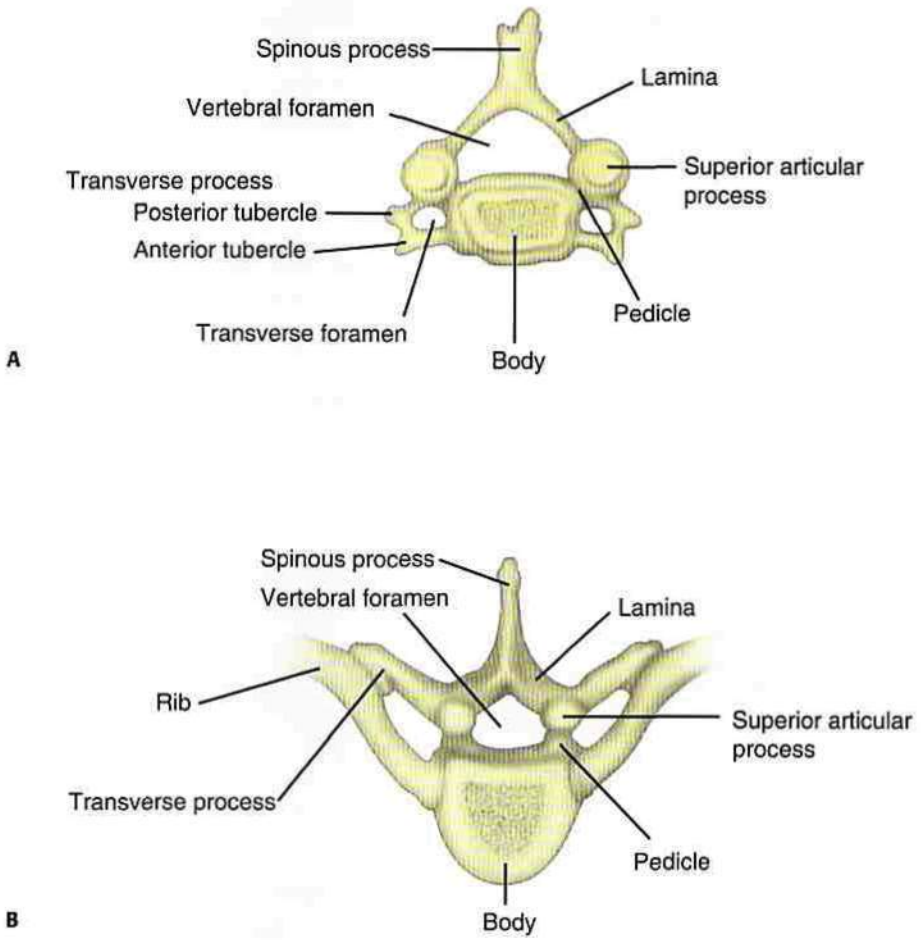


FIGURE 5-9. A typical cervical and a thoracic vertebra. (A) Cervical vertebra (B) thoracic vertebra.

arch posteriorly (made up of pedicles and laminae that serve to protect the spinal cord), and seven processes that serve different functions:

- The **spinous process** projects posteriorly and has the function of muscle attachment and movement.
- The two **transverse processes** project posterolaterally and have the same function as the spinous process.
- Four **articular processes** (two superior, two inferior) project from the same place as the transverse processes, but serve to guide movement.

These 33 vertebrae are divided into five areas, each area with a specific curvature:

- Cervical:
  - C1–C7.
  - Secondary curve resulting from the infant lifting its head.
- Thoracic:
  - T1–T12.
  - Primary curve from fetal development.
  - **Kyphosis** is an exaggeration of this curve that can be due to osteoporosis (leading to wedge fractures) or disk degeneration.

- Lumbar:
  - L1–L5.
  - Secondary curve resulting from walking.
  - **Lordosis** is an exaggeration of this curve that can be due to pregnancy, excess abdominal fat, or spondylolisthesis (see below).
- Sacral:
  - S1–S5.
  - Primary curve from fetal development.
- Coccyx = 4 fused vertebrae.

Excessive lateral curvature of the vertebral column is called **scoliosis.** The vertebrae also rotate such that the spinous processes move toward the abnormal curvature. Scoliosis can result from different lengths of the lower limbs, hemivertebra (in which half of a vertebra does not develop), and weakness of intrinsic back muscles on one side (known as myopathic scoliosis). The most common form of scoliosis is idiopathic and may have a genetic contribution.

Between each vertebra (except the C1–C2 space) is an intervertebral disk which serves as a shock absorber and distributes weight. Each disk is made up of an outer fibrous ring known as the **anulus fibrosus,** and an inner gelatinous mass known as the **nucleus pulposus.**

FLASH BACK

Spondylolisthesis is a cause of **lordosis.** Due to the failure of the pedicles to form properly, one or more of the lumbar vertebral bodies are free to move anteriorly, causing exaggerated curvature.

Pelvis

The pelvis is made up of two **hip bones** (each consisting of an **ischium**, **ilium**, and **pubis** that join to form the **acetabulum**, which articulates with the femur), the **sacrum**, and the **coccyx.**

The pelvis is divided into the **greater pelvis** (false pelvis) and **lesser pelvis** (true pelvis) by the pelvic inlet. The **pelvic inlet** is the plane passing through the S1 vertebral body (the **sacral promontory**) and the **terminal lines** (including the pubic crest, iliopectineal line, and arcuate line of the ilium). The **pelvic outlet** is the plane passing through the pubic symphysis anteriorly, the inferior pubic rami and ischial tuberosities laterally, and the coccyx posteriorly.

FLASH FORWARD

Dystocia, or abnormal/difficult labor, can be caused by the inability of the infant to pass through the pelvic inlet. The pelvic inlet may be too small (especially in android and platypelloid shaped pelvis) or the baby too large (macrosomia).

The greater pelvis is superior to the pelvic inlet and contains abdominal organs such as the ileum and sigmoid colon. It is bound by the abdominal wall anteriorly, the iliac crests laterally, and L5/S1 posteriorly.

The lesser pelvis lies between the pelvic inlet and pelvic outlet. It contains the pelvic viscera (thus making it the "true pelvis") including the urinary bladder, uterus, and ovaries. The pelvic diaphragm lies inferiorly (see Figure 5-10).

Upper Limbs

Each upper limb is made up of four basic skeletal segments:

- Pectoral girdle: Scapula, clavicle
- Arm: Humerus
- Forearm: Ulna (medial), radius (lateral)
- Hand: Carpus, metacarpus, phalanges

KEY FACT

The clavicle is the first long bone to ossify and the last of the epiphyses to fuse completely. Ossification starts at around 5–6 weeks in embryonic development and does not finish until somewhere between the ages of 25 and 31 years.

It is important to know how the nerves in the arm relate to the various parts of the humerus. The **axillary nerve** runs along the **surgical neck** of the humerus. The **radial nerve** runs in the **radial groove**, as the name suggests. The **median nerve** runs along the **distal humerus.** The **ulnar nerve** runs posterior to the **medial epicondyle** (making this nerve responsible for the "funny bone" sensation).

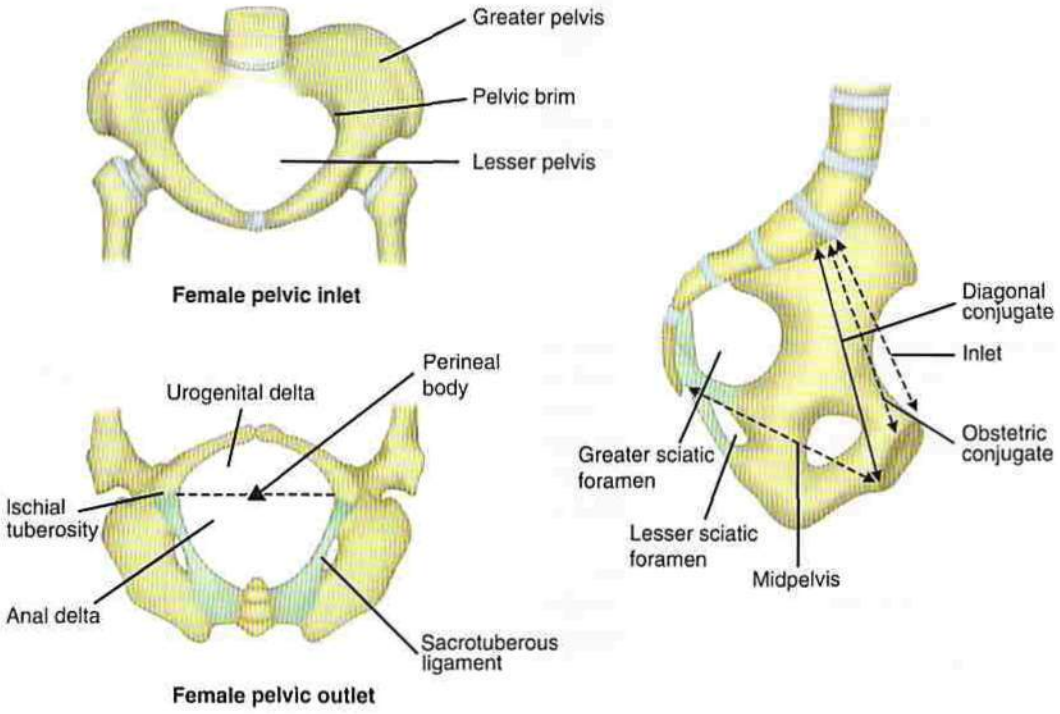


FIGURE 5-10. Views of the bony pelvis. (Modified, with permission, from White JS, *USMLE: Road Map: Gross Anatomy*, 2nd ed, New York: McGraw-Hill, 2006: 105.)

Lower Limbs

Like the upper limbs, each lower limb is made up of four basic segments:

- Pelvic girdle: Hip
- Thigh: Femur
- Leg: Tibia (anteromedial), fibula (posterolateral)
- Foot: Tarsus, metatarsus, phalanges

MNEMONIC

The Fibu**LA** is **LA**teral.

KEY FACT

Because the center of ossification at the distal end of the femur appears just before birth, medical investigators are able to use this radiographic finding along with others in cases of potential infanticide or criminal abortion to determine the age and viability of the fetus.

Common Injuries and Disorders

Fractures of the Skull

There are several different types of skull fractures.

- **Linear** skull fractures are the most common and usually result from blunt trauma. **Basilar** skull fractures are usually linear and most often involve the temporal bone. Signs of basilar skull fractures are "raccoon eyes" (blood collecting in the orbits), Battle's sign (blood collecting behind the ears), blood in the sinuses, and CSF leakage through the nose and ears.
- **Comminuted** fractures occur when the bone is broken into several pieces, some of which can lacerate the brain.
- **Depressed** fractures occur when the bone is depressed inward, putting pressure on and causing damage to, the brain.
- A **contrecoup** fracture occurs at the side opposite of the impact.

Fractures and Dislocations of the Vertebrae

Fractures and/or dislocations are usually due to **hyperflexion of the neck**, often resulting from car accidents or direct trauma to the back of the head. The most common injury is a crush or compression fracture of the vertebral body. Because the articular surfaces of cervical vertebrae are inclined horizontally, anterior dislocations can occur in this region of the spine without concomitant fractures. On the other hand, in the thoracic and lumbar regions,

articular surfaces are arranged vertically, so dislocations are usually seen with fractures.

Atlantoaxial Dislocation

The dens of the axis (C2) interlocks with the atlas (C1) through a foramen and is normally held in place by the cruciform, alar, and apical ligaments, as well as the tectorial membrane (a continuation of the posterior longitudinal ligament). When trauma or rheumatoid arthritis causes a tear in the cruciform ligament, the dens is able to move and may damage the cervical spinal cord and medulla, often resulting in quadriplegia.

Herniation of the Nucleus Pulposus

Also known as a "herniated disk" or "slipped disk," this occurs when the nucleus pulposus actually pushes into or through the anulus fibrosus **posterolaterally**, compressing spinal nerve roots and causing back pain. This commonly occurs at the lumbar level, but may occur in the cervical region as well.

- In the elderly, degeneration and wear at the posterior longitudinal ligament and posterior aspect of the anulus fibrosus in the lumbar region may allow the nucleus pulposus to herniate through. Nerve root impingement at the L5/S1 intervertebral foramen level can result in low back pain known as **lumbago** as well as pain radiating down the back of the thigh into the leg, called **sciatica.**
- Similar injuries in the cervical spine are also very common. **Hyperflexion** of the neck during head-on collisions may cause rupture of the posterior ligaments and subsequent nucleus pulposus herniation at the C5–C7 levels, resulting in pain in the neck radiating to the shoulders, and arms. Hyperextension of the neck, or **whiplash**, may stretch the anterior ligaments and cause fractures and dislocations of the vertebrae as well.

Spondylolysis

Spondylolysis is a defect or fracture in the **pars interarticularis,** (i.e., the part of the vertebral arch lamina that connects the inferior and superior articular processes.) Though it is frequently asymptomatic, it can cause lower back pain at the L5 level. While genetics probably play a role, it is thought that repeated microtrauma to this region may cause stress fractures. If the defects are bilateral, this condition can progress to **spondylolisthesis,** in which the affected vertebra becomes anteriorly displaced (see Figure 5-11). This is more common in men than women. Spondylolysis can be diagnosed with X-ray imaging.

Ankylosing Spondylitis

This inflammatory condition is a chronic, progressive, seronegative arthritis that commonly affects the lumbar vertebrae and sacroiliac joints. The anulus fibrosus of several vertebrae may become ossified leading to the characteristic "**bamboo spine**" seen on plain films. This disease mainly affects young males and often presents as low back pain that causes awakening from sleep, as well as morning spinal stiffness. Most patients with ankylosing spondylitis are **HLA-B27-positive.** Extraspinal manifestations can include peripheral arthritis (especially in the hips and knees), iritis, and pulmonary involvement.

See Table 5-2 for definitions and common features.

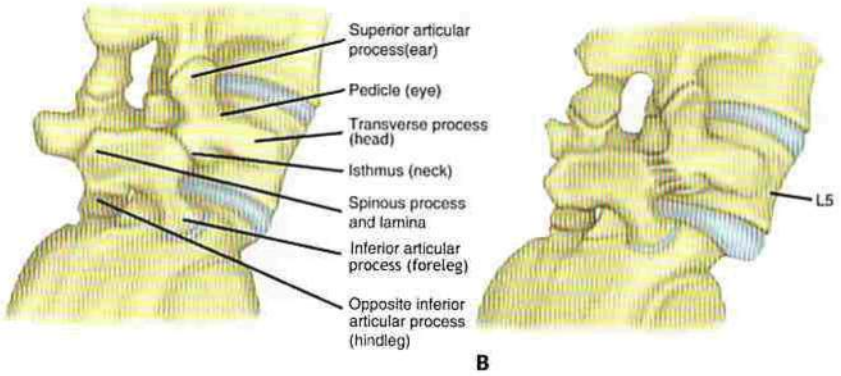


FIGURE 5-11. A comparison of spondylolysis and spondylolisthesis. (A) Posterior oblique radiographic view mimics shape of Scotty dog. In simple spondylolysis, dog appears to be wearing a collar. (B) In spondylolisthesis, Scotty dog appears decapitated. L5 body and disk are displaced anteriorly. (Modified, with permission, from White JS, *USMLE: Road Map: Gross Anatomy*, 2nd ed, New York: McGraw-Hill, 2006: 26.)

Fractures of the Pelvis

May occur from anteroposterior compression, lateral compression, and acetabular fractures.

- Anteroposterior compression (i.e., compression between the steering wheel and seat in automobile accidents) results in fractures of the pubic symphysis and pubic rami.
- Lateral compression can also involve the pubic rami as well as the alae of the ilium.
- Acetabular fractures can result from falls onto the feet with extended legs, causing the head of the femur to push through (protrusio acetabuli). Pelvic organs, vessels, and nerves may also be injured by the femur. Signs of pelvic fracture on exam include pelvic tenderness, palpable instability, and vaginal or urethral bleeding.

Fractures of the Upper Limb

Fractures can occur at many places along the arm, often with concurrent damage to important arteries and nerves. Knowledge of the anatomic relationships of the structures of the arm as well as the clinical consequences of nerve damage in the arm is useful for the exam. The following fractures are important to know.

- **Clavicle:** Most commonly in the middle one-third of the bone. The SCM muscle lifts the proximal piece, and the weight of the arm pulls down the distal piece.
- **Greater tuberosity:** Often associated with **separation of the shoulder.**
- **Surgical neck of the humerus:** May injure the **axillary nerve.**

TABLE 5-2. Synopsis of Spondylolysis, Spondylolisthesis, and Ankylosing Spondylitis

Spondylolysis	Spondylolisthesis	Ankylosing Spondylitis
Defect/fracture in the pars interarticularis that can cause back pain.	Anterior displacement of a vertebra commonly caused by spondylolysis or degenerative disk disease.	Inflammation of the sacroiliac joint and/or lumbar vertebrae that causes back stiffness, pain, and limited range of motion; moves cephalad and eventually affects the cervical spine.

- **Distal half of the humerus:** May injure the **radial nerve.**
- **Humerus, just superior to the elbow:** May injure the **brachial artery** and **median nerve.**
- **Medial epicondyle:** May injure the **ulnar nerve.**
- **Distal radius (Colles' fracture):** Often includes a fracture of the ulna (styloid process). A common finding is **"dinner fork" deformity** (dorsal displacement of bone fragments distal to the fracture).
- **Scaphoid:** Very little displacement of the bones; often missed on X-rays and misdiagnosed as a sprain. X-rays should be repeated in 10 days to confirm a suspected fracture. Whereas a sprain can be treated with rest and ice, fractures usually require casting. Improperly treated fractures may progress to a nonunion, avascular necrosis, and arthritis.

Fractures of the Lower Limb

As in the upper limb, fractures may occur throughout the lower limb.

- **Femoral neck:** This occurs more often in women than in men due to the greater risk of **osteoporosis**. The blood vessels that supply the femoral head are frequently ruptured in this fracture, resulting in **avascular necrosis.** On presentation, the lower limb is usually shortened and laterally rotated.
- **Tibial fractures:** Several types of fractures can occur at the middle of the body of the tibia. A **compound fracture** can involve both the tibia and fibula, and fragments of the tibia may tear blood vessels and penetrate the skin. **Diagonal fractures** may occur due to severe torsion of the lower leg. **Transverse fractures** or "boot-top" fractures are comminuted fractures that often occur after a forward fall while skiing, in which the leg is bent over the tops of the rigid boots. **Stress fractures** are transverse and may occur in normally sedentary people who decide to take a long walk or run.
- **Pott's fracture:** This occurs when the **medial** (deltoid) **ligament** is overly stretched during severe **foot eversion.** The strong medial ligament does not tear, but causes **fractures of the medial malleolus** (transverse avulsion) **and fibula** (oblique at the level of the joint).
- **Fracture of the fifth metatarsal:** Occurs during extreme **inversion** of the foot. This tears the **lateral ligament** and can fracture the **lateral malleolus.** This is a common sports injury.

Coxa Valga and Coxa Vara

The angle between the shaft of the femur and the head of the femur varies among people of different ages and genders. When this angle is large, it is termed coxa valga and when it is too acute, it is called coxa vara. The latter can lead to a shortening of the leg, making it difficult to completely abduct the leg.

Legg-Calvé-Perthes Disease

Avascular necrosis of the capital femoral epiphysis of the femoral head that causes decreased ROM and upper leg pain, typically in male children aged 3–12 years. The cause is unknown. It is self-limited because the bone eventually revascularizes, but the prognosis may be complicated by osteoarthritis (OA).

Slipped Epiphysis of the Femoral Head

If an adolescent has a weakened epiphyseal plate due to acute trauma or many microtraumas, the femoral head epiphysis can slowly slip away from the femoral neck, causing a coxa vara. This condition commonly affects obese adolescents during their growth spurt, and the slipped femoral head will present with hip pain **referred to the knee.** Diagnosis is made with an X-ray.

JOINTS

Types of Joints

Joints are simply defined as those areas where bones meet. There are three main types of joints: **Synovial, cartilaginous,** and **fibrous.** Each has a different form and function.

Synovial Joints

These joints are the most common in the body and allow for free movement between the two articulating bones. Allowing for this movement is lubricating fluid known as **synovial fluid** found in the **joint cavity** between the two bones. This cavity is enclosed by two structures: **articular cartilage** at the surface of the bone ends, and a **synovial membrane** that, in conjunction with an outer **fibrous capsule,** makes up the **articular capsule.** The periosteum of the two meeting bones blends together with the articular capsule. These joints are often strengthened by surrounding ligaments, which are especially important when considering common joint injuries.

There are six main types of synovial joints (see Table 5-3).

Cartilaginous Joints

FLASH BACK

The hyaline cartilage in primary cartilaginous joints is made up predominantly of type II cartilage.

Two types of cartilaginous joints exist in the body throughout development. **Primary cartilaginous joints** are usually temporary articulations of bone made up of **hyaline** cartilage that are, for example, present during development of the long bones and at epiphyseal plates. **Secondary cartilaginous joints** are made up of **fibrocartilage.** An example of this joint type is the intervertebral disks that join the vertebrae together and allow for limited movement of the spine.

TABLE 5-3. Types of Synovial Joints

Type of Synovial Joint	Examples	Type of Movement
Plane joints	Acromioclavicular joint	Gliding in one axis.
Hinge joints	Elbow joint	Flexion/extension.
Saddle joints	Carpometacarpal joints	Flexion/extension, abduction/adduction, circumduction.
Condyloid joints	Metacarpophalangeal joints	Same as saddle joints, with one axis usually greater than the other.
Ball and socket joints	Hip joint	Flexion/extension, abduction/adduction, circumduction, medial/lateral rotation.
Pivot joints	Atlantoaxial joint	Rotation (pronation/supination as in the radius; rotation of the atlas around the dens in the atlantoaxial joint).

Fibrous Joints

These are joints in which the articulating bones are connected by ligaments or fibrous membranes. Movement in these joints may be limited or nonexistent, depending on the fibrous limitations connecting the bones. Examples include the sutures of the skull, the pubic symphysis, and the joint connecting the radius and the ulna.

KEY FACT

Force from the hand to the humerus is transferred from the radius to the ulna through the interosseous ligaments, which are oriented in an inferomedial direction to transfer these pulling forces.

Major Joints and Common Injuries

Vertebra

- **Atlanto-occipital:** Synovial joint between the atlas (C1) and the occipital condyles that allows the head to nod "yes."
- **Atlantoaxial:** Synovial joint between the atlas (C1) and the axis (C2) that allows the head to shake "no" from side to side.
- **Facet joints:** Synovial joints between the inferior and superior articular facets of the spine.

Shoulder

- **Acromioclavicular joint**: A plane type of synovial joint between the lateral end of the clavicle and acromion of the scapula. Despite the strong ligaments keeping it in place, this joint may become separated following a fall onto the shoulder or outstretched arm.
- **Glenohumeral**: Ball-and-socket type of synovial joint between the humeral head and glenoid fossa. Because this fossa is shallow, the humeral head may be dislocated anteriorly or posteriorly. **Anterior dislocation** may result in damage to the **axillary nerve.**

Elbow

This hinge-type synovial joint is actually made up of three different joints:

- **Humeroulnar:** Reinforced by the medial collateral ligament.
- **Humeroradial:** Reinforced by the **lateral collateral ligament.**
- **Radioulnar:** Reinforced by the **annular ligament**. A **pulled elbow**, or nursemaid's elbow, may occur when a child is lifted forcibly by the arms while the forearm is pronated. This tears the annular ligament and causes subluxation of the radial head. Pain results from pinching of the annular ligament in the elbow joint, and pronation/supination becomes very limited. The elbow is reduced by supinating the forearm while the elbow is flexed.

KEY FACT

The Colles' fracture involves the distal radius and frequently the styloid process of the ulna as well. Bone fragments are displaced dorsally distal to the fracture, causing what is known as the dinner fork deformity.

Wrist

- **Radiocarpal joint:** A condyloid type of synovial joint between the radius and carpal bones. The most common type of fracture at this site is from a **FOOSH** (**F**all **O**n **O**ut**S**tretched **H**and), which leads to a **Colles' fracture** ("dinner fork" deformity).

Hip

This joint is a ball-and-socket joint between the femoral head and acetabulum. Fractures involving this area have been discussed previously.

Knee

The knee joint, a hinge-type synovial joint between the tibia, femur, and patella, is a favorite of the Step 1 exam. It is important to understand the relationships between the ligaments and menisci around this joint.

- **Medially:** The fibrocartilagenous **medial meniscus** is firmly attached to the **medial (tibial) collateral ligament.** Trauma to the lateral side of the knee will often result in injury to both of these structures.
- **Laterally:** The **lateral meniscus** is fibrocartilage that is **not** firmly attached to the **lateral (fibular) collateral ligament.** Trauma to the medial side of the knee may result in injury to the lateral ligament. Tears of the lateral meniscus are less common since it has fewer points of attachment.
- **Anteriorly:** The **anterior cruciate ligament** starts at the anterior tibia and extends posterolaterally to the lateral condyle of the femur. This ligament prevents anterior movement of the tibia when the knee is flexed. A tear of this ligament can be demonstrated with a positive **anterior drawer sign,** in which the doctor flexes the knee and pulls on the tibia, causing abnormal anterior displacement.
- **Posteriorly:** The **posterior cruciate ligament** starts at the posterior tibia and extends anteromedially to the medial condyle of the femur. This ligament prevents posterior movement of the tibia when the knee is flexed. A tear of this ligament can be demonstrated with a positive **posterior drawer sign,** in which the doctor flexes the knee and pushes on the tibia, causing abnormal posterior displacement.

A common soccer injury, called the **"unhappy triad,"** occurs when an athlete is hit from the lateral side and twists the flexed knee. The **tibial ligament** tears first, followed closely by the **medial meniscus**, and finally the **anterior cruciate ligament.** In this case, one would see abnormal passive abduction and a positive anterior drawer sign.

Ankle

- **Talocrural joint.** This is a hinge-type synovial joint between the ends of the tibia/fibula and the talus. **Inversion** (foot rolls in) results in sprain (tearing) of the **lateral ligament.** Extreme **eversion** (foot rolls out) places stress on the **medial ligament,** and may result in a **Pott's fracture** of the fibula and medial malleolus as discussed previously.

MUSCULAR SYSTEM

Types of Muscle

There are three basic types of muscle fibers that allow the human body to move, as well as providing form and heat: **skeletal, smooth,** and **cardiac.**

Skeletal

Most skeletal muscles produce movements of the skeleton, as the name implies, and are attached to bone or cartilage either directly or via tendons. There are many exceptions to this, however, such as eye muscles, superficial facial muscles, and the diaphragm. Also called "striated" muscle because of its parallel striations, skeletal muscle fibers are large, unbranched, and may contain several nuclei. Nerve impulses in the somatic nervous system innervate muscle fibers to cause contraction. This is often under voluntary control, though some skeletal muscles, such as the diaphragm, are under involuntary control.

Though new muscle cells can be formed to a limited degree, the primary growth response (i.e., to exercise) is through hypertrophy (increase in size, not number).

Smooth

Smooth muscle, on the other hand, lacks the striations of skeletal and cardiac muscles and is found mainly within the walls of visceral organs and the tunica media of blood vessels. Smooth muscle cells are small and spindle-shaped and have one central nucleus per cell. Unlike skeletal muscle, their contractions are slow and rhythmic, helping to move food **(peristalsis)** and regulate the flow of blood **(vasoconstriction)**, in addition to other functions **(sphincteric activity)**. Like cardiac muscle, the autonomic nervous system innervates smooth muscle and contraction is involuntary. Smooth muscle cells can undergo hypertrophy and hyperplasia.

KEY FACT

Smooth muscle is found mainly in the digestive tract and blood vessels, but it is also found at the base of hair follicles (erector pili muscles) and in the iris and ciliary body of the eye.

Cardiac

Cardiac muscle, as the name implies, composes the muscle of the heart (i.e., myocardium). The cells are striated and contain a single (sometimes two) central nuclei. They are often branched and are connected to other cardiac cells by **intercalated disks.** Actions of these cells are involuntary but are also under the control of specialized intrinsic pacemaker cells (in the SA and AV nodes) that are influenced by the autonomic nervous system. Unlike skeletal or smooth muscles, cardiac muscle cannot regenerate, though hypertrophy can result from increased demand on the heart (i.e., HTN).

Important Muscles

Head and Neck Muscles

Mastication muscles. There are four main muscles that move the mandible for chewing, all of which are innervated by various branches of CN V_3 (the mandibular branch of the trigeminal nerve):

- **Temporalis:** Elevates and retracts the mandible (closes the jaw).
- **Masseter:** Elevates and protrudes the mandible (closes the jaw).
- **Medial pterygoid:** Elevates and helps (slightly) to protrude the mandible (closing and grinding the jaw).
- **Lateral pterygoid:** Depresses (slightly) and protrudes the mandible as well as moves it from side to side (opening and grinding the jaw).

MNEMONIC

Three muscles CLOSE the jaw (the **M**s **M**unch): **M**asseter, **M**edial pterygoid, and te**M**poralis.
One muscle OPENS the jaw (the **L** **L**owers): **L**ateral pterygoid.

The main force that opens the jaw is gravity, though the lateral pterygoid as well as suprahyoid and infrahyoid muscles assist.

Muscles with "glossus" and "palat." As a general rule, all of the muscles that end in "glossus" are innervated by CN XII (hypoglossal nerve), and all of the muscles that have "palat" in them are innervated by CN X (vagus nerve). The following muscles follow these rules:

- **Genioglossus:** CN XII; depresses and protrudes the tongue.
- **Hypoglossus:** CN XII; depresses and retracts the tongue.
- **Styloglossus:** CN XII; retracts and elevates the tongue for swallowing.
- **Levator veli palatini:** CN X; elevates the soft palate for swallowing/yawning.
- **Palatopharyngeus:** CN X; tenses the soft palate and moves the pharynx for swallowing.

There is one exception to each rule: The **palatoglossus** muscle, which elevates the posterior tongue **and** brings the soft palate to the tongue, follows the "palat" rule ("palat" is first in palatoglossus) and is innervated by the vagus nerve. The **tensor veli palatini**, which tenses the soft palate and opens the auditory tube during swallowing/yawning, does **not** follow the "palat" rule, but

MNEMONIC

All muscles that end with **GLOSSUS** (except the palatoglossus—"palat" is first!) are innervated by the hypo**GLOSSAL** nerve.

All muscles with **PALAT** are innervated by the **VAGUS** (except the tensor veli palatini, which is too **TENSE** to be with the rest).

FLASH BACK

The second through fourth branchial clefts usually merge and involute; when the second branchial cleft persists, a fistula can be formed between the pharynx and skin. This fistula is usually located along the anterior border of the upper third of the SCM.

instead is innervated by a branch of CN V_3 (mandibular branch of the trigeminal nerve).

Sternocleidomastoid. The SCM muscle attaches superiorly to the mastoid and divides inferiorly into two heads that form attachments to the sternum and clavicle. Contraction of one SCM tilts the head to the ipsilateral side while flexing and rotating the head to the contralateral side. The SCM is important for both anatomic and clinical reasons:

- It divides the neck anatomically into anterior and posterior triangles.
- It is an important landmark for branchial anomalies that may occur during embryologic development (see flashback).
- Congenital torticollis occurs when the SCM is congenitally shortened or injured at birth, causing a fixed tilted, rotated, and flexed position.
- Spasmodic torticollis (a.k.a. "cervical dystonia" or "wry neck") occurs with abnormally increased tone in the SCM. It is often associated with spasms of intense neck pain.

Larynx. The muscles of the larynx are divided first into extrinsic and intrinsic groups. The **extrinsic muscles** function to **move the hyoid bone and larynx superiorly or inferiorly**, while the **intrinsic muscles** make fine adjustments to the **vocal folds** and **rima glottidis** to aid in speaking, whispering, and respiration.

The extrinsic laryngeal muscles are further divided into **suprahyoid** and **infrahyoid** muscles (see Table 5-4). The suprahyoid muscles and **stylopharyngeus** elevate the hyoid and larynx, while the infrahyoid muscles depress these structures.

The intrinsic laryngeal muscles work together to alter the shape and tension of the vocal folds in order to change the size and shape of the space between the folds, called the rima glottidis. Dividing them into functional groups is helpful:

- Adductors (close the rima glottidis for phonation):
  - Lateral cricoarytenoid muscles: Main adductors.
  - Transverse and oblique arytenoid muscles: Adductors and sphincters to protect during swallowing.
  - Aryepiglottic muscles: Sphincters.
- Abductor (open the rima glottidis for breathing):
  - Posterior cricoarytenoid muscles: The **only abductors** of the intrinsic muscles of the larynx (without these muscles, we would be unable to breathe!).

TABLE 5-4. Extrinsic Muscles of the Larynx

Suprahyoid Muscles	Infrahyoid Muscles
Mylohyoid	Sternohyoid
Geniohyoid	Omohyoid
Stylohyoid	Sternothyroid
Digastric	Thyrohyoid

- Tensors (raise the pitch of the voice):
  - Cricothyroid muscles.
- Relaxers (decrease the pitch of the voice, and used for singing):
  - Thyroarytenoid muscles.
  - Vocalis muscles (for fine adjustments).

Almost all motor innervation of the inner laryngeal muscles comes from **below** via the **recurrent laryngeal nerve** (a branch of the **inferior** laryngeal nerve). Damage to the recurrent laryngeal nerve therefore causes hoarseness (if unilateral), and possible breathing difficulties and aphonia (if bilateral). Damage may occur following surgery, including thyroidectomy or compression from laryngeal cancer.

All sensory innervation comes from **above** via the **internal laryngeal nerve** (a branch of the **superior** laryngeal nerve). Damage to the superior laryngeal nerve therefore causes anesthesia of the laryngeal mucosa. This is dangerous as foreign bodies are more likely to pass, but this nerve is often temporarily blocked in order to pass an endotracheal tube. Laryngeal elevation is the primary mechanism for preventing aspiration during swallowing.

KEY FACT

The cricothyroid muscle is the one exception to this rule. **Both** its motor and sensory innervation comes from **above** via branches of the superior laryngeal nerve: the external branch for motor and the internal branch for sensory.

Upper Limb Muscles

Rotator cuff muscles. There are four muscles collectively known as the rotator cuff muscles that help to stabilize the humeral head in the glenohumeral joint while the shoulder moves.

- **Supraspinatus:** Innervated by the suprascapular nerve; also helps the deltoid muscle to abduct the arm for the first 15°.
- **Infraspinatus:** Innervated by the suprascapular nerve; laterally rotates the arm.
- **Teres minor:** Innervated by the axillary nerve; laterally rotates the arm.
- **Subscapularis:** Innervated by subscapular nerves; medially rotates the arm.

MNEMONIC

Rotator cuff muscles: **SItS.** **S**upraspinatus, **I**nfraspinatus, **t**eres minor, **S**ubscapularis (small "t" for teres **minor;** also the only rotator cuff muscle not innervated by a scapular nerve).

Arm/forearm muscles. The muscles of the arm and forearm are divided into anterior and posterior compartments. Knowing the innervation and actions of these muscles is extremely important—this knowledge enables clinicians to predict how patients will present following different types of trauma.

FLASH BACK

It may be helpful to review the brachial plexus (in the neurology chapter) at this time.

The **anterior compartment of the arm** contains three **flexor** muscles, all innervated by the **musculocutaneous nerve:**

- **Biceps brachii:** Flexes and supinates the forearm.
- **Brachialis:** Flexes the forearm.
- **Coracobrachialis:** Flexes and adducts the arm.

The **posterior compartment of the arm** contains only one **extensor** muscle, innervated by the **radial nerve:**

- **Triceps brachii:** Extends the forearm.

The **anterior compartment of the forearm** contains **pronators** of the forearm and **flexors** of the forearm, hand, and fingers. All are innervated by the **median nerve,** except the flexor carpi ulnaris and the medial part of the flexor digitorum profundus, which are innervated by the **ulnar nerve.**

The **posterior compartment of the forearm** contains **extensors** and **supinators** (with the exception of the brachioradialis, which flexes the forearm). All are innervated by the **radial nerve.**

KEY FACT

The adductor pollicis has different innervation than the rest of the thenar muscles (the ulnar nerve instead of the recurrent median nerve).

THENAR/HYPOTHENAR. Thenar muscles control actions of the thumb and are innervated by the median nerve (**except** the adductor pollicis, which is innervated by the ulnar nerve):

- **Abductor pollicis brevis:** Abduction
- **Opponens pollicis:** Opposition
- **Flexor pollicis brevis:** Flexion
- **Adductor pollicis**

Hypothenar muscles control actions of the fifth digit and are innervated by the ulnar nerve:

- **Opponens digiti minimi:** Opposition
- **Flexor digiti minimi:** Flexion
- **Abductor digiti minimi:** Abduction

MNEMONIC

THenar muscles for the **TH**umb.

NERVE DAMAGE AFFECTING THE MUSCLES OF THE UPPER LIMB

- **Fracture of the surgical neck of the humerus** or **shoulder dislocation** damages the **axillary nerve** resulting in weakness or loss of function of the deltoid and teres minor. Thus, the patient is unable to abduct and laterally rotate the arm.
- A **midhumeral fracture** damages the **radial nerve** in the radial groove. This will affect the extensors in the forearm but **not** the triceps, as the fracture is usually distal to this innervation. The tell-tale sign of this fracture is a **wrist drop.**
- Damage to the **musculocutaneous nerve** is usually via a weapon, not trauma, and will affect the flexors of the arm. The patient will not be able to flex the elbow, and supination of the forearm will be weak.
- In **supracondylar fractures of the humerus** (near the elbow), the **median nerve** may be injured causing weak wrist flexion and the inability to flex digits 1, 2, and 3, and pronate the forearm. Digits 4 and 5 are spared because they are supplied by the medial part of the flexor digitorum profundus, which is innervated by the **ulnar nerve.** Thus, when trying to make a fist, the patient can only flex digits 4 and 5, making the "**hand of benediction.**"
- **Carpal tunnel syndrome** results from entrapment of the median nerve in the carpal tunnel at the wrist. Risk factors include repetitive wrist flexion, female gender, obesity, and any condition leading to increased edema (e.g., hypothyroidism or pregnancy). Symptoms include reduced sensation in the lateral three and a half digits, weakness of thumb flexion and abduction, and loss of thumb opposition. Sensation is intact on the medial one and a half fingers because the superficial branch of the median nerve is spared.
- **Fracture of the medial epicondyle of the humerus** ("funny bone") can damage the **ulnar nerve**, leading to impaired adduction of the fingers and thumb, as well as impaired flexion of the fourth and fifth digits, leading to a claw-hand deformity. Also, upon flexing the wrist, the hand moves toward the radial (lateral) side due to unopposed action of the flexor carpi radialis.

MNEMONIC

For the actual order of the muscles, remember **A OF A OF A:**

Thenar, lateral to medial:
Abductor pollicis brevis
Opponens pollicis
Flexor pollicis brevis
Adductor pollicis

Hypothenar, lateral to medial:
Opponens digiti minimi
Flexor digiti minimi
Abductor digiti minimi

KEY FACT

The adductor pollicis is the only thenar muscle innervated by the ulnar nerve.

Lower Limb Muscles

GLUTEAL MUSCLES. This region of the body contains two main groups of muscles.

The glutei mainly extend and abduct the thigh and are innervated by the gluteal nerves:

- **Gluteus maximus: Inferior gluteal nerve;** extends thigh.
- **Gluteus medius and minimus: Superior gluteal nerve;** abducts and medially rotates the thigh.

The smaller muscles of the gluteal region are covered by the gluteus maximus and help to **laterally rotate** the thigh:

- **Piriformis:** Ventral rami of S1 and S2.
- **Obturator internus:** Nerve to obturator internus (L5, S1).
- **Gemelli superior and inferior:** L5 and S1.
- **Quadratus femoris:** Nerve to quadratus femoris (L5, S1).

THIGH/LEG MUSCLES. Like the arm/forearm muscles, the thigh and leg muscles are organized into compartments. The thigh muscles are organized into three compartments: Anterior, medial, and posterior; the leg muscles are organized into anterior, lateral, and posterior compartments.

The **anterior compartment of the thigh** contains **flexors of the hip** and **extensors of the knee.** Most of them are innervated by the **femoral nerve,** though there are exceptions noted below.

- **Pectineus:** Flexes, adducts, and helps to medially rotate the thigh.
- **Iliopsoas:** Innervated by ventral rami of lumbar nerves (psoas) along with the femoral nerve (iliacus); flexes the hip.
- **Tensor of fascia lata:** Innervated by the superior gluteal nerve; flexes, abducts, and medially rotates the thigh, and keeps the knee extended.
- **Sartorius:** Flexes, abducts, and laterally rotates the thigh, and flexes the knee.
- **Quadriceps femoris:** Extends the knee and helps to flex the thigh.

The **medial compartment of the thigh** contains the **adductors of the thigh** and is innervated by the **obturator nerve:**

- **Adductor longus:** Adducts the thigh.
- **Adductor brevis:** Adducts and helps to flex the thigh.
- **Adductor magnus:** Adducts the thigh; various parts help to either flex or extend the thigh.
- **Gracilis:** Adducts the thigh; flexes and medially rotates the leg.
- **Obturator externus:** Laterally rotates the thigh.

The **posterior compartment of the thigh** contains the **hamstrings,** which are **extensors of the thigh and flexors of the leg** and are innervated by the **sciatic nerve.**

The **anterior compartment of the leg** contains **dorsiflexors of the ankle** and **extensors of the toes.** All are innervated by the **peroneal nerve** or **deep fibular nerve.**

- **Tibialis anterior.**
- **Extensor digitorum longus.**
- **Extensor hallucis longus.**
- **Peroneus tertius:** Also helps to evert the foot.

The **lateral compartment of the leg** contains the **adductors of the thigh** and is innervated by the **obturator nerve:**

- **Adductor longus:** Adducts the thigh.
- **Adductor brevis:** Adducts and helps to flex the thigh.
- **Adductor magnus:** Adducts the thigh; various parts help to either flex or extend the thigh.
- **Gracilis:** Adducts the thigh; flexes and medially rotates the leg.
- **Obturator externus:** Laterally rotates the thigh.

KEY FACT

In 12% of people, the sciatic nerve splits and one branch pierces the piriformis. Compression leads to "piriformis syndrome," which is common in mountain climbers that develop hypertrophic piriformis muscles.

KEY FACT

The sciatic nerve innervates the entire leg except the inner medial calf. As such, sciatica and piriformis syndrome spares the part of the leg innervated by the saphenous nerve, the termination of the femoral nerve ($L_{2,3,4}$).

The **posterior compartment of the leg** contains the **plantar flexors of the ankle** and **flexors of the toes** (exceptions noted below) and are innervated by the **tibial nerve:**

- **Gastrocnemius.**
- **Soleus.**
- **Plantaris.**
- **Popliteus:** Flexes the knee.
- **Flexor hallucis longus.**
- **Flexor digitorum longus.**
- **Tibialis posterior:** Also helps to invert the foot.

Nerve damage affecting the muscles of the lower limb. Piriformis syndrome: The sciatic nerve enters the greater sciatic foramen very closely related to the piriformis muscle (usually the nerve is inferior to the muscle, though it can occasionally pierce the muscle or run superiorly). Some people who use the muscles in the gluteal region extensively (e.g., skaters, mountain climbers, and cyclists) can overdevelop their piriformis muscle resulting in pinched-nerve, sciatica-like symptoms. Women are more susceptible.

The **Trendelenburg's sign** occurs following damage to the **superior gluteal nerve** (affecting the gluteus medius and minimus). To test for this, observe the patient's back while the patient raises each foot off the ground. If the right pelvis falls when the right foot is lifted, the **left** superior gluteal nerve is damaged; if the left pelvis falls when the left foot is lifted, the **right** superior gluteal nerve is damaged. This sign can also occur in patients with a hip dislocation or fracture of the neck of the femur.

Trauma in the femoral triangle region may damage the **femoral nerve,** causing weakened ability to flex the thigh (weak iliacus and sartorius), as well as loss of extension of the thigh (quadriceps femoris muscle).

Injury to the **tibial nerve** is uncommon in the popliteal region because it runs deep (though deep knife wounds can injure it). Symptoms include loss of flexion of the leg, loss of plantarflexion of the ankle, and loss of flexion of the toes and inversion of the foot. There may also be loss of sensation on the sole of the foot.

The **common fibular (peroneal) nerve** is the most commonly injured nerve in the lower leg because of its superficial course around the fibular neck, a common fracture site. Damage results in loss of function of all muscles in the anterior and lateral compartments, resulting in inability to dorsiflex the foot, evert the foot, and extend the toes. This is known as a **footdrop** and the patient will develop a high-stepping gait to compensate.



I 8 10 EGGs AT 12:

IVC at T**8**.
T**10:** Esopha**G**us and va**G**us.
Aorta/Azygos and Thoracic duct at T**12.**



C3, 4, 5 keeps the diaphragm alive!

Diaphragm

The diaphragm separates the thoracic and abdominal cavities and is the most important muscle for inspiration. Important structures pass through the diaphragm at various levels.

- T8: The IVC passes through.
- T10: Esophagus and vagus nerve.
- T12: The aorta, thoracic duct, and azygos vein.

Cervical nerves C3, C4, and C5 make up the somatic **phrenic nerve.** Irritation of the diaphragmatic pleura or peritoneum causes pain that is referred to the shoulder.

Physiology

MUSCLE TYPES

The musculoskeletal system and connective tissues of the body contain three specialized types of muscle cells:

- **Skeletal:** Comprising voluntary, striated muscles.
- **Smooth:** Comprising involuntary muscles, primarily of visceral organs, and vasculature.
- **Cardiac:** Comprising the contractile tissues of the heart.

Each muscle cell type performs the specific function of contraction. Using proteins located in the cytoplasm, these cells, under neural control, increase or decrease their length in a coordinated fashion.

FLASH BACK

Cardiac muscle physiology is covered in the cardiovascular chapter.

Skeletal Muscle

Overview

Each skeletal muscle fiber receives neural input from a motor neuron via the **neuromuscular junction.** A single motor neuron and the muscle fiber it innervates are known as a **motor unit.** Large motor units in large muscle groups execute coarse movements (e.g., the quadriceps muscles) and small motor units control fine movements (e.g., extraocular muscles).

FLASH BACK

Acetylcholinesterase is a common target for pharmacologic paralysis in neuromuscular blockade.

In the synaptic cleft, the action potential (AP) that has propagated along the neuron is transferred to the **myocyte**, or muscle cell. This transfer occurs via the neurotransmitter **acetylcholine (ACh)** released from the axonal bouton (see Figure 5-12). The myocyte's postsynaptic membrane, known as the **motor end plate**, contains specialized **nicotinic ACh receptors.** These receptors are transmembrane cation channels (Na^+ and K^+) that open when bound to ACh. Activation of these ligand-gated channels results in increased local cation flux, leading to membrane depolarization that is propagated to the nearby **transverse tubule** (**T-tubule**) system (see Figure 5-13). Excess ACh is hydrolyzed by the enzyme **acetylcholinesterase**, which resides on the postsynaptic or postjunctional membrane, into acetate and choline. Choline is reabsorbed by the presynaptic neuron, via Na^+-coupled transport, for production of more ACh.

KEY FACT

Skeletal muscle is a structurally complex organ, containing several levels of organization. They are listed below, from smallest to largest:

- Myofilament
- Sarcomere
- Myofibril
- Muscle cells
- Muscle fiber
- Muscle fasciculus
- Whole muscle

Excitation-Contraction Coupling

Myofibrils are the functional components of contraction. The T-tubules, a system of plasma membrane invaginations (see Figure 5-13), allow the AP to propagate deep into the cytoplasm, facilitating Ca^{2+} release from the sarcoplasmic reticulum. This increase in intracellular calcium triggers **excitation-contraction coupling** among intracellular contractile proteins. These longitudinally-arranged contractile proteins comprise a complex known as the **sarcomere.** Repeating units of sarcomeres comprise **myofibrils** within a single multinucleate myocyte (see Figure 5-14).

Each myofibril contains interdigitating **thick** and **thin myofilaments.**

- Thick filaments contain a large-molecular-weight protein, **myosin**, which itself is made of heavy and light chains. The light chains contain **actin-binding sites** and an ATP cleavage site.

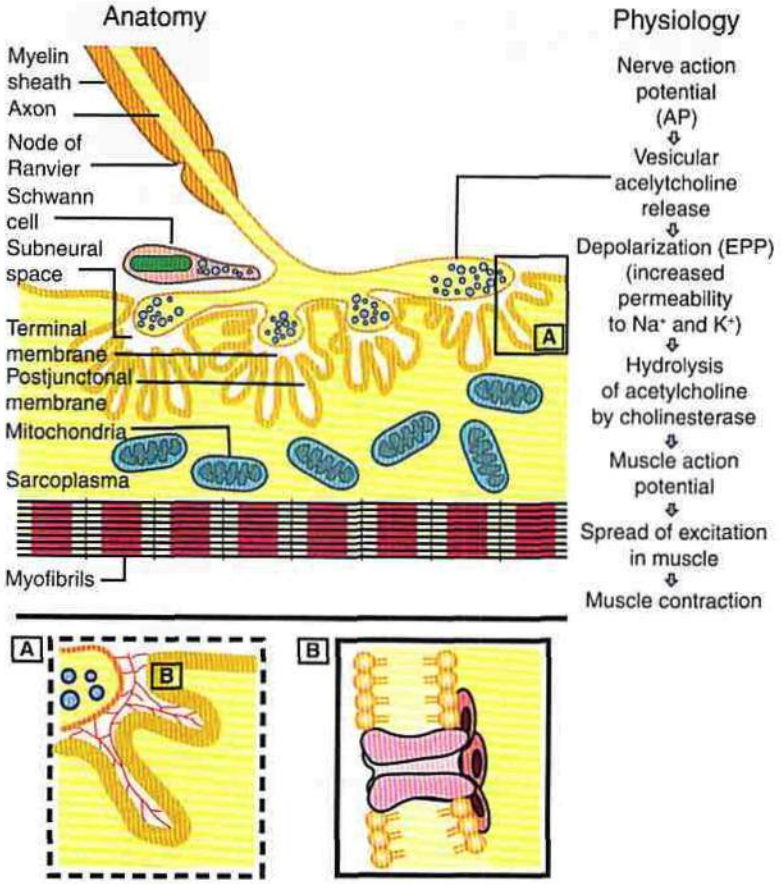


FIGURE 5-12. Structure of the motor end plate. The structure of the motor end plate is shown above on the left, while the sequence of events from liberation of ACh by the nerve AP to contraction of the muscle fiber are indicated by the right column. The insets are enlargements of the indicated structures. The highest magnification depicts the receptor in the bilayer of the postsynaptic membrane. (Modified, with permission, from Brunton LL, Parker KL, Buxton I, Blumenthal DK, *Goodman & Gilman's the Pharmacological Basis of Therapeutics*, 11th ed, New York: McGraw-Hill, 2006: 225.)

- Thin filaments have three components:
  - **Actin:** Bound by myosin, it contributes to **cross-bridge** formation that allows for movement of myosin filaments and change in myofibril length.
  - **Tropomyosin:** At rest, this protein occupies potential **myosin-binding sites** on the actin protein, preventing contraction.
  - **Troponin:** Ca^{2+} released from the sarcoplasmic reticulum binds troponin, inducing a conformational change that consequently moves tropomyosin, freeing actin's myosin-binding sites for contraction.

CLINICAL CORRELATION

A lack of ATP can keep the muscle in "twitch," leading to cramps and rigor mortis.

Once tropomyosin uncovers actin's myosin-binding sites, actin binds myosin light chains, creating **cross-bridges.** The myosin light chains pivot, causing the myosin heavy chain to slide along the actin filament. This event is known as a **twitch** and develops the tension that exerts force (proportional to the number of cross-bridges) during muscle contraction. Returning the pivoted or flexed myosin light chains to their original state requires the cleavage of ATP to ADP + P_i. Once regenerated, the myosin light chain binds a new molecule of ATP for future cross-bridge coupling (see Figure 5-14).

This process continues as long as the cytoplasmic Ca^{2+} concentration remains high. The Ca^{2+}-ATPase functions to ensure Ca^{2+} reuptake into the sarcoplas-

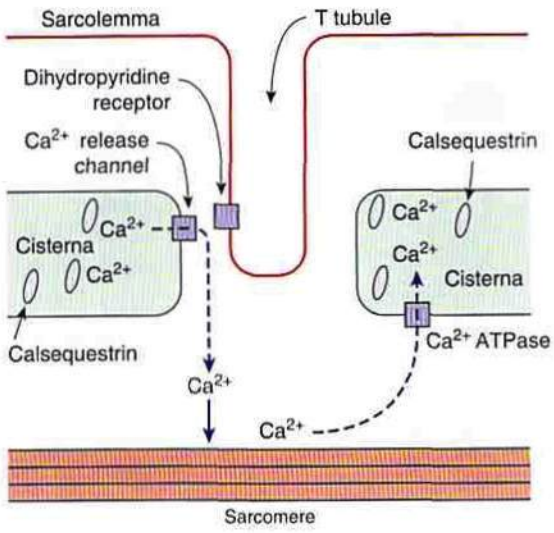


FIGURE 5-13. Schematic of transverse tubule system. Diagram of the relationships among the sarcolemma (plasma membrane), a T tubule, and two cisternae of the sarcoplasmic reticulum of skeletal muscle (not to scale). The T tubule extends inward from the sarcolemma. A wave of depolarization, initiated by ACh binding, is transmitted from the sarcolemma down the T tubule. It is then conveyed to the Ca^{2+} release channel (ryanodine receptor), perhaps by interaction between it and the dihydropyridine receptor, which are shown in close proximity. Release of Ca^{2+} from the Ca^{2+}-release channel into the cytosol initiates contraction. Subsequently, Ca^{2+} is pumped back into the cisternae of the sarcoplasmic reticulum by the Ca^{2+} ATPase (Ca^{2+} pump) and stored there, in part bound to calsequestrin. (Modified, with permission, from Murray RK, Granner DK, Rodwell VW, *Harper's Biochemistry*, 27th ed, New York: McGraw-Hill, 2006: 572.)

mic reticulum, thus reducing the cytoplasmic Ca^{2+} concentration. When the calcium concentration has returned to low levels, troponin returns to its original state and tropomyosin again blocks the myosin-binding sites on actin. If a muscle fiber is stimulated repeatedly without allowing sufficient time for Ca^{2+} to reaccumulate in the sarcoplasmic reticulum, the sustained high cytoplasmic Ca^{2+} concentration leads to sustained muscle contraction, or **tetanus.**

The sarcomere is the most basic contractile unit. Under light microscopy, it appears as a series of bands and lines (see Figures 5-15 and 5-16 and Table 5-5), spanning the space between **Z lines.**

Within a given muscle, the maximum force or tension that can be produced is dependent upon the length of the muscle. The tension a muscle is able to produce is proportional to both the number of cross-bridges formed and the number that *could* be formed. At the extremes of myofibril length (very long and very short) either the number of existing cross-bridges or the number of available new cross-bridges is limited, thus reducing the tension the muscle fiber can produce.

Smooth Muscle

Overview

Smooth muscle differs from skeletal muscle in at least three important ways. Firstly, the myofilaments are not organized into sarcomeres, and thus do not appear striated. Secondly, innervation is primarily via the autonomic nervous system, not the somatic nervous system. And thirdly, the excitation-contraction cascade within smooth muscle differs from that of skeletal muscle. These differences allow smooth muscle to perform its functions more efficiently than skeletal muscle could.

FLASH BACK

Clostridium tetani induces tetanus via an exotoxin that maintains high intracellular Ca^{2+}.

MNEMONIC

Contraction results in **HIZ** shrinkage: H, I, and Z bands shorten during muscle contraction, while the A band's length remains constant.

KEY FACT

Smooth muscle locations:
Vasculature (larger than capillaries)
Airways (larger than terminal bronchioles)
GI tract
Urinary bladder and ureters
Uterus
Muscles within the eye

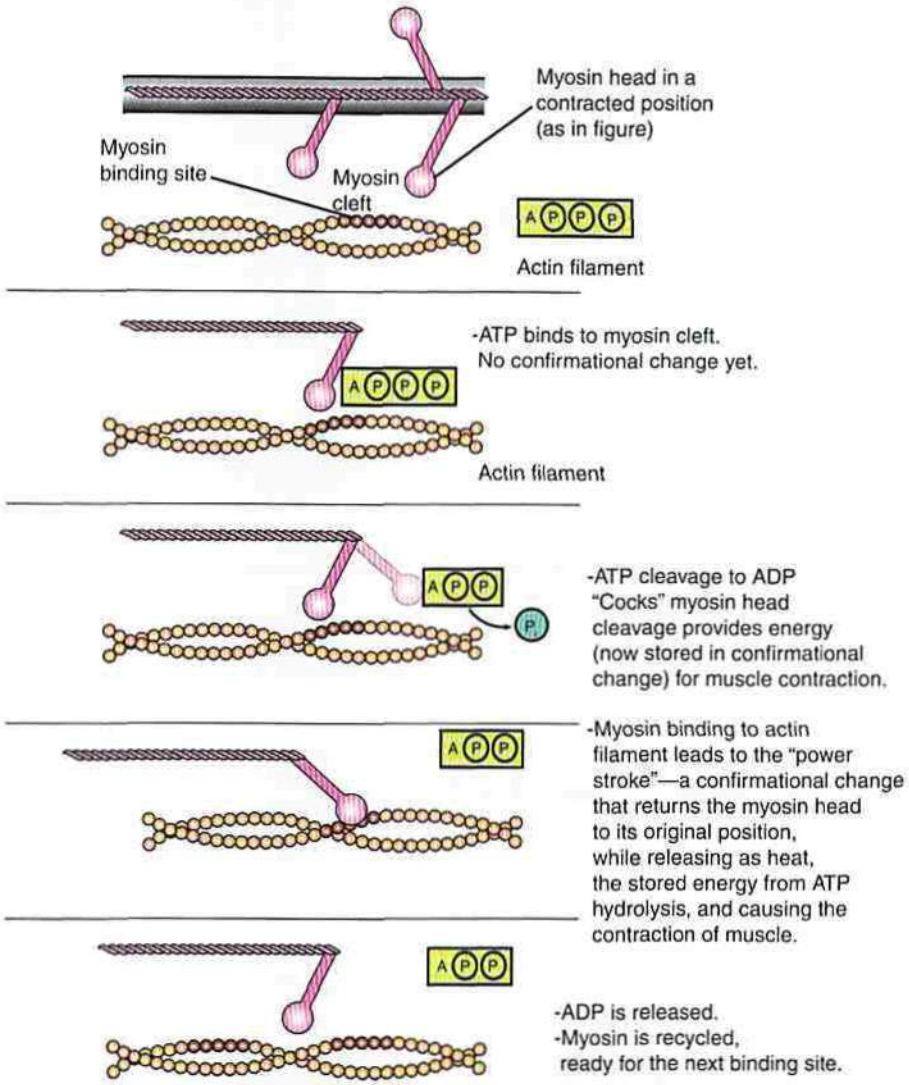


FIGURE 5-14. Myofibrils and excitation-contraction coupling.

EXCITATION-CONTRACTION COUPLING

Smooth muscle lacks troponin. Instead, the protein **calmodulin** acts as the cross-bridging gatekeeper (see Figure 5-17). Similar to skeletal muscle, the cascade begins with an AP. This leads to opening of voltage-gated Ca^{2+} channels and an increase in the intracellular Ca^{2+} concentration. Calmodulin then binds Ca^{2+} and activates **myosin light chain kinase (MLCK)**, which in turn phosphorylates myosin. Activated myosin is able to bind and release actin, repeatedly forming and breaking cross-bridges. Like skeletal muscle, each cycle consumes one molecule of ATP.

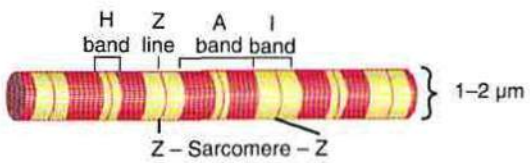


FIGURE 5-15. Myofibril.

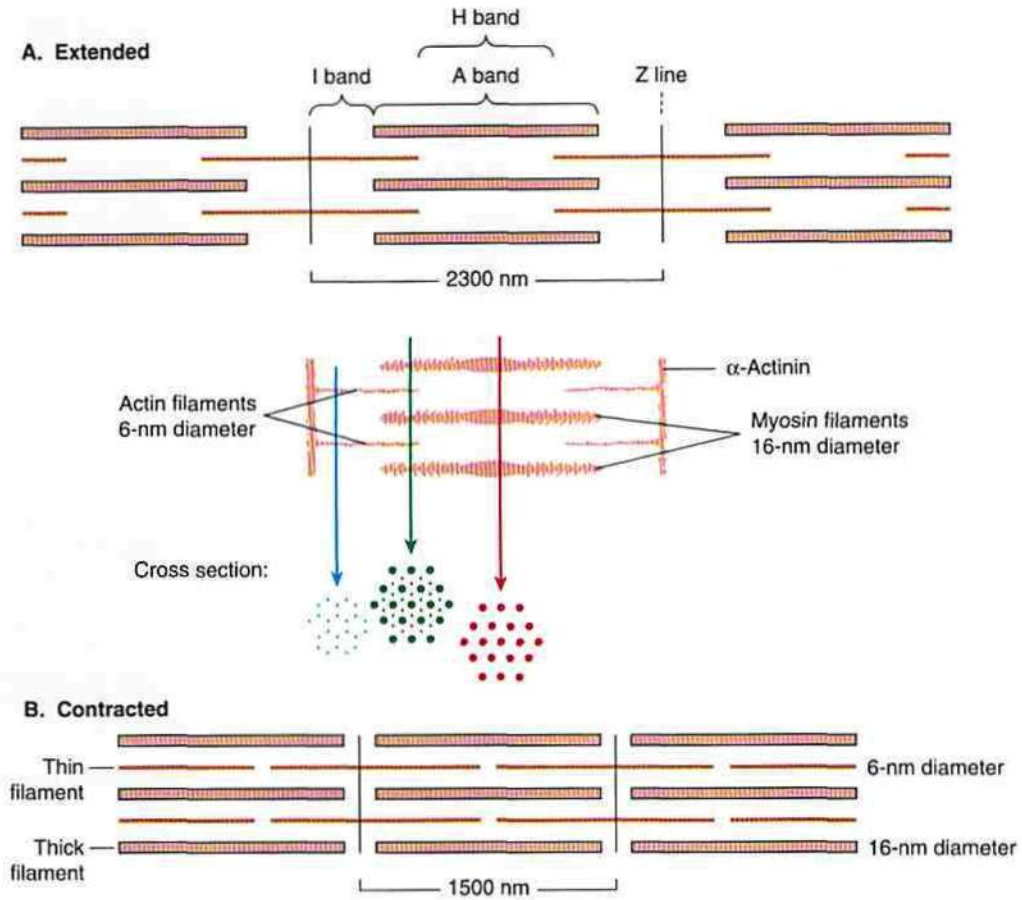


FIGURE 5-16. Arrangement of thick and thin filaments in the sarcomere. (Modified, with permission, from Murray RK, Granner DK, Rodwell VW, *Harper's Biochemistry*, 27th ed, New York: McGraw-Hill, 2006: 567.)

However, when the Ca^{2+} concentration decreases (again due to a Ca^{2+}-ATPase), and myosin is dephosphorylated via **myosin light chain phosphatase**, the dephosphorylated form of myosin can still interact with actin via **latch-bridges**. These are residual attachments that allow for the maintenance of tonic tension within smooth muscle without consuming energy. In this way,

TABLE 5-5. Bands of the Sarcomere Visible With Polarized Light Microscopy

A band	Dark bands at the center of the sarcomere, composed of myosin filaments; this region has the potential for cross-bridge formation, so thin and thick filaments may overlap here.
I band	Lightly staining and adjacent to A bands, composed of actin filaments and Z lines; their width decreases with contraction.
Z line	Darkly staining, at the center of I bands, marking the boundaries of a single sarcomere.
H zone	At the center of the A band, cross-bridging does not occur here.
M line	Darkly staining, at the center of the H zone, proteins here link adjacent myosin filaments together.

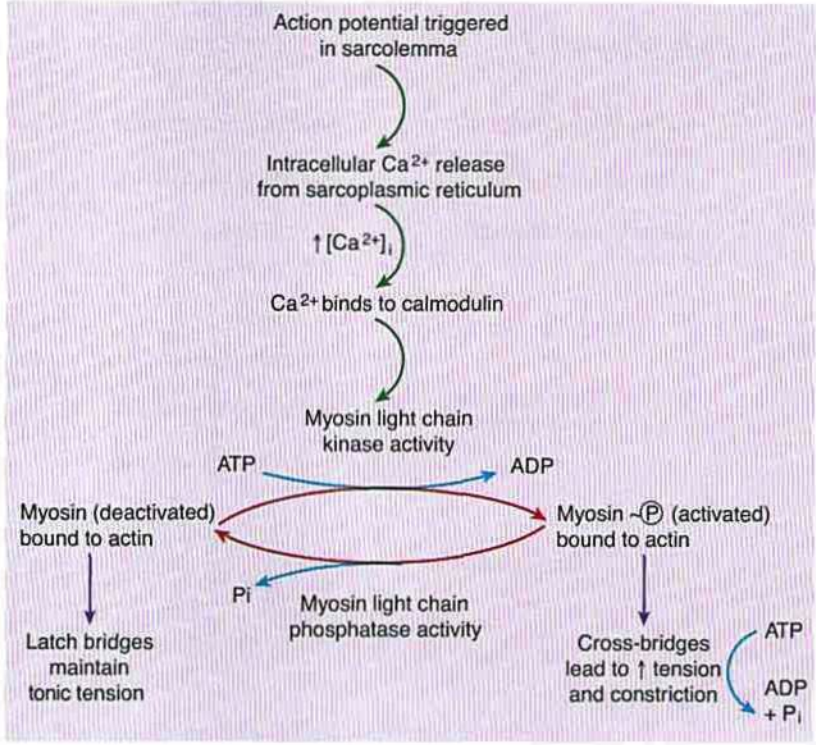


FIGURE 5-17. Diagram of smooth muscle contraction.

(unlike skeletal muscle) smooth muscle can maintain tonic contraction without continually cleaving ATP. When combined with **gap junctions**, these capabilities allow smooth muscle to produce the coordinated tonic contractions necessary for aiding digestion, maintaining BP, voiding urine, and accomplishing labor and delivery.

METABOLISM

Cross-bridging of skeletal muscles requires a constant supply of ATP. At rest, muscles may be responsible for 30% of the body's O_2 consumption, while during exercise this number tops off at around 90%. The major energy source that fuels muscle contraction is **carbohydrate metabolism.** Secondary sources of energy include **fatty acid** and **amino acid metabolism.**

GLUCOSE

In the well-fed state, glucose is readily available to supply the energy needs of muscle. Therefore, simple glycolysis, coupled with the Krebs' cycle, can meet the needs of muscles. Following a carbohydrate-rich meal, an increase in the intracellular transport of glucose occurs via insulin signaling. Each glucose molecule is immediately phosphorylated (to glucose-6-phosphate) upon entering the cell, and then shuttled into glycolysis.

FLASH BACK

The structure of glycogen and the regulation of hepatic glycogen metabolism were introduced in the biochemistry section.

GLYCOGEN

As the major storage form of glucose, glycogen is essential to **anaerobic glycolysis** in active muscle. The main storage sites of glycogen are the liver and skeletal muscles. Hepatic glycogen sustains the blood glucose level while muscle glycogen provides a readily available source of glucose during muscle contraction.

Regulation of glycogen metabolism occurs on two levels:

- Allosteric enzymatic regulation.
- Hormonal regulation by insulin.

Allosteric Regulation

Glycogen synthase, the enzyme responsible for intramuscular glycogen production, is allosterically favored by increased levels of the substrates of glycogen synthesis, such as glucose-1-phosphate. Simultaneously, **glycogen phosphorylase**, responsible for glycogen catabolism, is inhibited by glucose-6-phosphate and ATP, products of glycolysis and successful glycogen degradation.

In contrast, glycogen degradation occurs in the presence of molecules and messengers of muscle activity. Specifically, increased intracellular Ca^{2+} and **AMP** (a product of ATP hydrolysis) lead to enhanced glycogen phosphorylase activity. Once the muscle relaxes and Ca^{2+} returns to the sarcoplasmic reticulum or AMP is consumed to produce ATP, these effects are lost. The end result is that active muscle sends signals that increase the breakdown of glycogen into glucose, thus increasing available energy substrates.

Insulin Regulation

In the fed state, the body increases serum insulin levels. Specifically, in the liver, insulin depresses gluconeogenesis and increases glycogen production. Within skeletal muscle, insulin increases glucose transport into cells, where it is phosphorylated and enters metabolic pathways ending in ATP production. The absence of insulin exerts opposite effects. In this state, the liver mobilizes glycogen and adipose tissues mobilize fatty acids in order to maintain systemic glucose levels. Within muscles, a decrease in insulin-mediated glucose transport leads to glycogenolysis. More information on insulin's actions can be found in the endocrine physiology section in Chapter 2.

Lipid and Protein Metabolism

In a state of starvation, muscle is able to use fatty acids and ketones for energy. By the third week of starvation, muscle is able to operate almost entirely on mobilized fatty acids.

At the onset of a state of starvation, rapid muscle protein turnover also occurs, resulting in the release of amino acids to the liver for gluconeogenesis. As the brain begins to use alternative sources of energy, thus reducing its need for glucose, protein breakdown decreases.

Exercise

During strenuous activity, skeletal muscle's metabolic needs are the greatest. Depending on the intensity of the activity, potential energy sources (glucose, glycogen, fatty acids, and protein) are utilized in different proportions. When energy demands are greatest (i.e., during sprinting), anaerobic metabolism predominates. Intracellular glucose and glycogen are the primary fuels for rapid energy requirements. In fact, anaerobic metabolism can begin sustaining ATP stores before O_2 delivery to muscle increases. When energy needs are low, however (i.e., during walking), oxidation of circulating glucose and fatty acids is favored. This form of metabolism extracts far more energy from fuel (~ 38 ATP molecules per glucose molecule), and therefore can sustain muscle activity much longer than inefficient substitutes like anaerobic metabolism.

At the onset of aerobic exercise, hepatic glycogenolysis supplies ~ 40% of the increased energy needed by muscles. In these early stages, there is an exercise-

induced translocation of GLUT-4 glucose transporters to the muscle plasma membrane. This insulin-independent response is thought to be mediated by AMP kinase. As time progresses, hepatic gluconeogenesis becomes more important in the maintenance of circulating glucose. Alanine and lactate, produced in peripheral anaerobic metabolism, become important substrates. In fact, resting muscle can transform glycogen stores into lactate for systemic release, leading to hepatic conversion to glucose and redistribution to active muscle.

At later stages of lengthy exercise, glucose use within skeletal muscle decreases and fatty acid oxidation increases from its original ~ 60% share to provide nearly all of the necessary substrates for aerobic exercise metabolism.

IMPORTANT LABORATORY VALUES

TABLE 5-6. Laboratory Values Pertinent to Musculoskeletal and Connective Tissue Disorders

Lab Test	Abbreviation	Marker for...	Normal Range
Erythrocyte sedimentation rate	ESR	Systemic inflammation.	Male: 1–13 mm/h. Female: 1–20 mm/h.
Creatine kinase	CK	Muscle injury.	Male: 38–174 U/L. Female: 96–140 U/L.
CK isoenzyme (myocardial bound)	CK-MB	Cardiac injury or regenerating muscle.	≤ 5% of the total CK should be MB isoenzyme.
Antineutrophil cytoplasmic antibody	c-ANCA (cytoplasmic)	Wegener's granulomatosis.	Nonreactive.
	p-ANCA (perinuclear)	Microscopic polyangiitis **or** focal necrotizing and crescentic glomerulonephritis.	Nonreactive.
C-reactive protein	CRP	Direct marker for systemic inflammation.	< 12 mg/L.
Alkaline phosphatase	Alk phos	Bone turnover.	Age ≤ 18 years: ~ 330 U/L. Age > 18 years: ~ 100 U/L.
Serum calcium	Ca^{2+}	Disordered calcium homeostasis.	< 10 mg/L.
Parathyroid hormone	PTH	Parathyroid gland function.	3 Tests: Intact PTH: 10–65 pg/mL. PTH N-terminus: 8–24 pg/mL. PTH C-terminus: 50–330 pg/mL.
Parathyroid hormone-related peptide	PTHrP	Protein secreted by neoplastic cells, mimics PTH; its activity may lead to disordered calcium and/or phosphate homeostasis.	Undetectable

Pathology

SKELETAL ONCOLOGY

The most common tumor found in bone is a metastasis from other organ systems. Prostate, breast, and lung carcinomas account for 80% of bone metastases. The majority of these metastases spread hematogenously, although rarely, these cancers can invade bone through local invasion. Once in the bone, tumors may lead to osteolysis, osteogenesis, or both. Factors that elicit bone resorption, such as **parathyroid hormone-related peptide** (PTHrP) or cytokines that increase osteoclast differentiation and activation (IL-1 or TNF-α) result in osteolysis. Conversely, osteogenesis occurs in response to lesions that stimulate osteoblastic differentiation.

Presentation

Although they are often asymptomatic, bony metastases may present with pain, swelling, nerve compression, or pathologic fracture. Marrow infiltration by lymphomas, one type of **myelophthisis**, is also common. Pain usually develops gradually over several weeks, and is most intense at night. If neurologic symptoms such as numbness, weakness, or radiculopathy accompany back pain, an emergent spinal cord evaluation is indicated.

Diagnosis

All patients should be screened with plain films and serum calcium levels. Osteolytic lesions > 1 cm in size, common in renal cancer, can regularly be detected with plain radiographs and often cause **hypercalcemia.** Urinary collagen degradation products (such as hydroxyproline) are indicative of ECM breakdown. Osteoblastic lesions, commonly seen in breast and prostatic metastases, are best detected with radionucleotide bone scans which will show increased uptake. In these instances plain films may reveal focal sclerosis. These patients often have increased serum alkaline phosphatase levels and, if disease is widespread, hypocalcemia.

Treatment

The therapeutic approach depends on the source of the underlying malignancy and symptomatology. Bisphosphonates, agents that inhibit osteoclast function, are adjunctive medications used to preserve bone health and relieve pain. Severe bone pain in the terminal stages of cancer is very common and adequate attention to pain symptoms may require relatively high doses of narcotic analgesics to maintain patient quality of life.

Prognosis

Overall survival is highly variable, depending on the primary diagnosis.

MNEMONIC

Primary tumors that metastasize to bone: **BLTT** with a **C**ool **K**osher **P**ickle.

Breast
Lung
Thyroid
Testes
Colon
Kidney
Prostate

KEY FACT

The three most common bony sites for metastases (in descending order):

- Vertebrae
- Proximal femur
- Pelvis

MNEMONIC

Lung = **L**ytic
Prostate = Blastic
Breast = **B**oth lytic and blastic

Primary Cancers

Benign

There are four important benign primary tumors of bone.

- **Osteochondroma:** The most common benign bone tumor, usually occurring in men under age 25 years. It often arises from the long metaphysis. Malignant transformation to chondrosarcoma is rare.
- **Giant cell tumor:** Benign tumor composed of spindle-shaped cells with multinucleated giant cells (osteoclasts). It is most commonly found at epiphyseal ends of long bones, such as the distal femur or the proximal tibia.

The peak incidence is at 20–40 years of age. It carries a distinct histologic appearance (see Figure 5-18). Grossly it contains areas of necrosis and hemorrhage. It also has a characteristic "double bubble" or "soap bubble" appearance on X-ray.

- **Enchondroma:** Benign cartilage cyst found within the bone marrow, often affecting the hand, humerus, femur, and tibia. On X-ray, this tumor appears as a lytic area in the bone marrow with stippled calcification. On MRI, this tumor has a popcorn appearance.
- **Osteoid osteoma:** A benign bone-forming tumor seen in adolescence. It typically presents with night pain that improves with NSAID use.

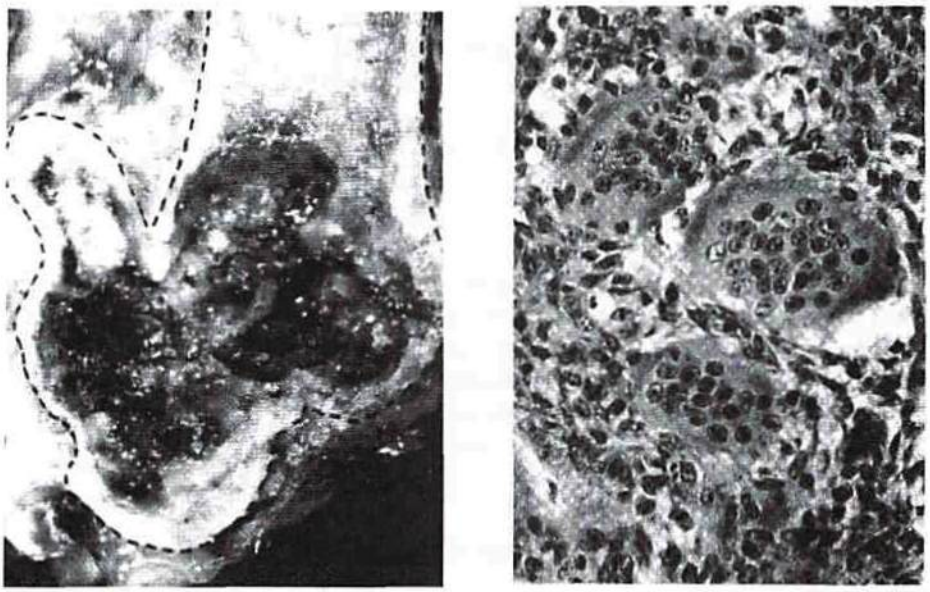
MALIGNANT

There are three important malignant primary bone tumors:

- Osteosarcoma
- Ewing's sarcoma
- Chondrosarcoma

Osteosarcoma

The most common primary bone malignancy (45%), this cancer results in the production of unmineralized bone **(osteoid)** and is therefore also known as **osteogenic carcinoma** (see Figure 5-19). The majority of cases occur in children and adolescents. Those that occur late in life (~ 10%) are often secondary to predisposing risk factors such as radiation exposure, familial retinoblastoma, benign transformation (as in Paget's disease), or bone infarction. Males are affected more than females.



A B

FIGURE 5-18. Giant cell tumor pathology. (A) Giant cell tumor of the distal end of the femur, showing expansion of the bone end by a well-circumscribed mass composed of fleshy tumor that has replaced the bone. A thin rim of bone is present around the mass. The outline of the bone is indicated by the dotted lines. (B) Histology of giant cell tumor of bone, showing numerous osteoclast-like giant cells and intervening small spindle cells. (Reproduced, with permission, from Chandrasoma P, Taylor CR, *Lange Pathology*, 3rd ed, Stamford, CT: Appleton & Lange, 1998. Copyright © 2006 McGraw-Hill.)

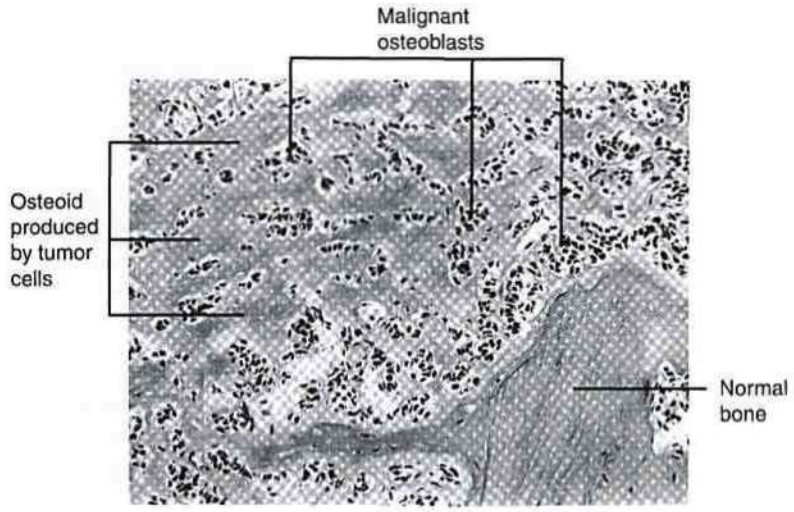


FIGURE 5-19. Histology of malignant osteosarcoma. Histology showing small malignant osteoblastic cells surrounded by osteoid, which appears as a homogeneous material between the malignant cells. Contrast this with the residual normal bone spicule. (Reproduced, with permission, from Chandrasoma P, Taylor CR, *Lange Pathology*, 3rd ed, Stamford, CT: Appleton & Lange, 1998. Copyright © 2006 McGraw-Hill.)

Presentation

Osteosarcoma has an affinity for the metaphyses of long bones, specifically the distal femur, proximal tibia, and proximal humerus. Patients usually complain of pain and swelling of the affected region.

Diagnosis

A plain film will reveal osteolysis with a "moth-eaten" appearance and a periosteal "sunburst" reaction. New bone formation at the margin of the soft tissue mass leads to the characteristic **Codman's triangle** due to elevation of the periosteum. Chest radiography and CT are employed to rule out lung metastases and a bone scan can uncover bony metastases.

Treatment

Preoperative chemotherapy, limb-sparing surgery, and postoperative chemotherapy are the usual regimen. Prominently employed chemotherapeutics include doxorubicin, ifosfamide, cisplatin, and methotrexate with leucovorin.

Prognosis

The most important prognostic indicator is response to chemotherapy. Long-term survival in extremity sarcoma lies in the range of 60%–80%.

Ewing's Sarcoma

Comprising only 10%–15% of bone sarcomas, this anaplastic blue-cell tumor has its peak incidence in adolescents. The underlying genetic abnormality is overexpression of the **mic-2 gene,** whose product is a cell-surface marker. This occurs simultaneously with t(11;22) translocation, producing a chimeric protein of unknown function. This genetic abnormality is common in those with primitive neuroectodermal tumors (PNETs), the family of tumors to which Ewing's sarcoma belongs.

Presentation

Most often found in diaphyses of long bones, Ewing's sarcoma can also arise in flat bones.

Diagnosis

Radiography reveals a characteristic "onion-peel" periosteal reaction with a soft tissue mass (see Figure 5-20). Pathologic examination uncovers sheets of small, round, blue cells that can be confused with lymphoma or small cell carcinomas.

MNEMONIC

Going out for E**wings** and **onion** rings. (Ewing's sarcoma results in an onion-peel periostal reaction.)

Treatment

The foundation of treatment is systemic chemotherapy, typically pursued before surgery. Doxorubicin, cyclophosphamide, ifosfamide, etoposide, vincristine, and dactinomycin are all efficacious. Surgical resection then follows.

Prognosis

This condition is very aggressive and is treated as a systemic disease due to the high probability of early metastases. Common sites of metastasis include the lungs and other bones. Patients with disease of the distal extremities have a 5-year survival rate of 80%. Cure rates are higher in children under 11 years of age.



FIGURE 5-20. Radiography of Ewing's sarcoma. Radiography of periosteal response in Ewing's sarcoma of the femur in a 15-year-old boy. (Reproduced, with permission, from Skinner H, *Current Diagnosis & Treatment in Orthopedics*, 4th ed, New York: McGraw-Hill, 2006: 336.)

Chondrosarcoma

One-quarter of all bone sarcomas are chondrosarcomas, with a peak incidence in the fourth to sixth decades. Primarily arising in flat bones like the shoulder and pelvic girdle, these tumors typically develop de novo by sporadic mutation. Rarely, they deviate from this pattern appearing in the diaphyses of long bones or arising by malignant transformation of enchondromas or osteochondromas.

Presentation

Like other bone sarcomas, pain and swelling are the principal symptoms. New-onset pain, inflammation, and/or gradually growing mass, especially in the scapula or pelvis, are commonly associated with this tumor.

Diagnosis

Radiography reveals a lobular mass with mottled, punctate, or annular calcifications of the cartilaginous matrix.

Treatment

Nearly all chondrosarcomas are resistant to chemotherapy; surgical resection of primary tumors and metastases is the mainstay of therapy. Rare variants may have a component that can be treated with chemotherapy.

Prognosis

Chondrosarcomas follow an indolent course, eventually metastasizing to the lungs.

BENIGN MUSCULOSKELETAL DISEASE

Osteoarthritis

Arising from failure of the diarthrodial (movable, synovial-lined) joints, OA is the most common form of joint disease. While age is the strongest risk factor, trauma, obesity, and repetitive joint use also contribute to intra-articular mechanical wear and tear. As the name suggests, OA involves bony injury due to pitting and fraying of articular cartilage. Specifically, bony pathology may be present in some or all of the following forms.

- **Loss of articular cartilage:** Wear and tear leads to cartilaginous injury. As the cartilage wears, it is unable to self-repair, leading to changes in joint stress and architecture.
- **Sclerosis:** Increased mechanical stress transmitted to bone beneath an articular cartilage ulcer produces increased subchondral bone density. This hypertrophy appears as increased opacity on plain films.
- **Osteophytes:** Increased stress causes bone to remodel, producing bone spurs at the edges of articular surfaces.
- **Bone cysts:** Microfractures beneath the cortex form due to increased stress. The bone resorbs due to micromotion and the cyst fills with fluid and fibrous tissue.

MNEMONIC

Osteoarthritis leads to **SMASHED** joints:

Subchondral cysts
Mechanical damage to
Articular cartilage
Synovial
Hypertrophy
Eburnation
DIP joints = Heberden's nodes

KEY FACT

Affected DIP joints are known as **Heberden's nodes,** and affected PIP joints are known as **Bouchard's nodes.**

Soft tissue pathology may also include synovitis with mild hypertrophy and thickening of the joint capsule.

Primary OA is idiopathic and pathologically identical to secondary OA, which has an associated underlying cause.

Presentation

Older patients complain of a deep aching pain in weight-bearing diarthrodial joints after prolonged use, usually at the end of the day. This pain often improves with rest. On physical examination of the hands, pain and bony swelling are most pronounced in the distal and proximal interphalangeal (DIP and PIP) joints. Swelling and bony crepitus may be evident in affected joints (see Figure 5-21). Advanced disease may result in gross deformity, noticeable bony hypertrophy, partial dislocation (known as **subluxation**), and loss of joint motion. **There are no associated systemic symptoms.**

Diagnosis

Based on clinical and radiographic findings, joint space narrowing occurs early in disease progression. Subchondral bone may contain cysts or sclerosis. Sclerotic regions have an ivory-like appearance radiographically, representing a phenomenon called **eburnation**. An altered joint contour or subluxation can also be seen. Despite this list of possible changes, however, radiographic appearance often does not correlate with symptom severity. Laboratory tests are usually normal in primary OA, though synovial fluid analysis may be helpful in secondary OA (caused by calcium pyrophosphate dihydrate, gout, or septic arthritis).

Treatment

Treatment goals include reducing pain, maintaining mobility, and preventing disability. Reducing joint loading is a primary approach for mild OA. This may include improving posture, decreasing lumbar lordosis, and weight loss. OA is often the primary reason elderly patients avoid exercise; however, mod-

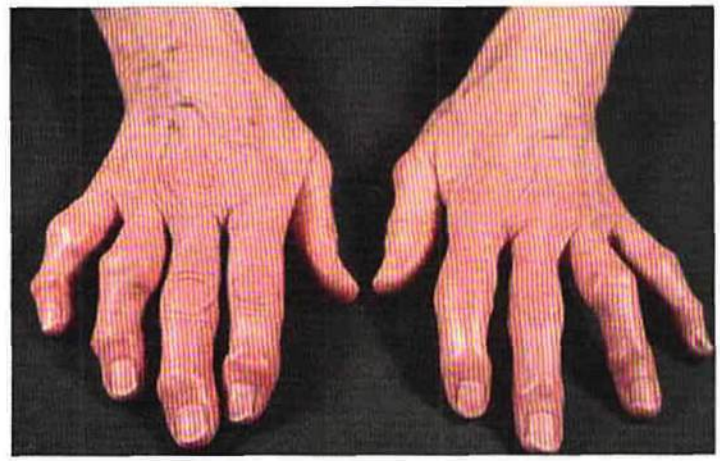


FIGURE 5-21. Osteoarthritic changes in the hand. Notice that anatomic changes, restricted to the DIP and PIP joints, do not affect the wrists. (Reproduced,with permission, from Fauci AS et al. [eds.]. *Harrison's Principles of Internal Medicine,* 17th ed, New York: McGraw-Hill, 2008.)

erate to vigorous exercise (enough to improve cardiovascular health) can be undertaken without exacerbating pain. In fact, physically active patients report decreased pain and increased quality of life.

NSAIDs and acetaminophen are palliative pain relievers but do not prevent disease progression. Other short-term interventions include tidal irrigation and glucocorticoid or hyaluronic acid injections. Reserved for patients who fail conservative therapy, these therapies inevitably only last a few months.

KEY FACT

Watch out for GI complications (peptic ulcer disease and/or hemorrhage) in patients regularly taking NSAIDs!

Prognosis

The natural history of OA is progressive joint degeneration and decreasing range of motion that worsens with age, use, and wear. End-stage OA can be relieved with total joint arthroplasty in hips, knees, and shoulders.

Rheumatoid Arthritis

RA is characterized by chronic autoimmune processes resulting in inflammatory synovitis of diarthrodial joints. This inflammation leads to reactive synovial hypertrophy, referred to as **pannus**, which causes bone and cartilage erosion within the affected joint. On light microscopy, pannus progression is accompanied by a synovial T_H1 cell infiltrate, edema, and microvascular injury. Though the inciting cause of RA is unknown, synovitis is propagated via T cells, B cells, mast cells, and circulating **anti-IgG** (also known as **rheumatoid factor, RF**) that deposits in synovial tissue. RF is actually pentameric IgM that recognizes the Fc portion of IgG. Local cytokine release also leads to fibroblast activation and release of degradative enzymes that damage articular surfaces. There is a strong genetic association with **HLA-DR4** haplotypes. RA is more common in women.

Presentation

Often affecting the PIP, metacarpophalangeal (MCP), and wrist joints, RA is marked by morning stiffness lasting > 1 hour, but **improving with use.** Typically, joint involvement is symmetrical, and arises following a prodrome of systemic complaints: fever, fatigue, and/or anorexia. Eventually the most striking symptoms become swelling, tenderness, warmth, and reduced range of motion in affected joints. Knee involvement can result in inflamed synovium within the popliteal fossa, creating the characteristic **Baker's cyst.** As the disease progresses, joint laxity, subluxation, and cartilage degradation develop. In late stages, fibrous or bony fusion, known as **ankylosis**, and soft tissue contractures may predominate. Specifically, fixed radial deviation of the wrists with ulnar deviation of the fingers is common, as are hyperextension or **swan-neck deformities** of the **PIP joints**, and **hyperextension** or **boutonnière deformities** of the **DIP joints** (see Figure 5-22).

Patients often suffer from a variety of extra-articular symptoms. Muscle weakness and atrophy are common adjacent to affected joints. Twenty percent of patients may develop **rheumatoid nodules:** centralized zones of necrotic tissue surrounded by macrophages and granulation tissue, appearing in areas of mechanical pressure. Rheumatoid arteritis, pleuritis, and pneumonitis can also occur in patients with high RF titers.

Diagnosis

RA is primarily a clinical diagnosis, although laboratory evaluation may reveal an elevated ESR and CRP, and a positive RF test (in two-thirds of RA patients). Patients also exhibit abnormal erythropoiesis and a normochromic, normocytic anemia with thrombocytosis. Synovial fluid tests reveal a turbid aspirate with increased protein and many PMNs.

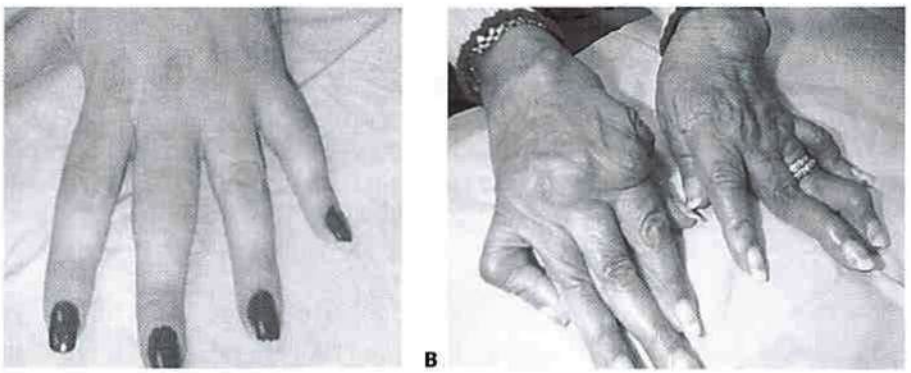


FIGURE 5-22. Manifestations of RA in the hand. (A) A patient with early RA; there are no joint deformities, but the soft tissue synovial swelling around the third and fifth PIP joints is easily seen. (B) A patient with advanced RA; severe joint deformities including dorsal wrist swelling, subluxation at the MCP joints, and swan-neck deformities (hyperextension at the PIP joints), are prominent. (Reproduced, with permission, from Imboden J, Hellmann DB, Stone JH, *Current Rheumatology Diagnosis & Treatment*, New York: McGraw-Hill, 2004: 163.)

Radiography, though not necessary for establishing the diagnosis, can confirm physician suspicions and reveal the extent of joint space narrowing (see Figure 5-23). Adjacent osteopenia and bone erosion are commonly seen.

In order to make the diagnosis of RA, a patient must fulfill four of the following seven criteria:

- Morning stiffness in and around the joints lasting >1 hour before maximal improvement.
- Simultaneous arthritis of three or more joint areas, observed by a physician, with soft tissue swelling or joint effusions, not just bony overgrowth. The 14 possible joint areas involved include the right or left PIP, MCP, wrist, elbow, knee, ankle, and metatarsophalangeal joints (see Figure 5-24).
- Arthritis of hand joints (wrist, MCP, or PIP joints).
- Symmetric arthritic joint involvement.
- **Rheumatoid nodules:** Subcutaneous nodules over bony prominences, extensor surfaces, or juxta-articular regions (observed by a physician).
- Elevated serum RF demonstrated by any method for which the result has been positive in less than 5% of normal control subjects.
- **Radiographic changes:** Typical changes of RA on posteroanterior hand and wrist radiographs that must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints.

KEY FACT

Elevated platelet counts can be a nonspecific sign of systemic inflammatory conditions.

Treatment

Therapeutic goals include (1) pain relief, (2) reduction of inflammation, (3) anatomic preservation, (4) functional maintenance, and (5) systemic control. Since the etiology is still unknown, therapeutic selection is often empirical. Physical therapy and rest are effective for pain relief, while orthotics can be used to support weakened joints.

Medical management includes five modalities:

- **Aspirin and NSAIDs:** Alleviate pain of inflammation but do not affect progression.
- **Low-dose oral or intra-articular glucocorticoids:** Reduce inflammation and bone erosion.
- **Disease-modifying antirheumatic drugs (DMARDs):** These include methotrexate, antimalarials, and sulfasalazine. They slow disease progres-



FIGURE 5-23. Radiography of a knee with RA. Symmetric loss of cartilage space is typical of an inflammatory arthritis. Despite this severe narrowing, there is very little subchondral sclerosis or osteophyte formation since these repair mechanisms are generally not functional in active RA. OA, in contrast, would produce unilateral joint space narrowing with a prominent osteogenic reaction (sclerosis and osteophytes). (Reproduced, with permission, from Imboden J, Hellmann DB, Stone JH, *Current Rheumatology Diagnosis & Treatment*, New York: McGraw-Hill, 2004: 165.)

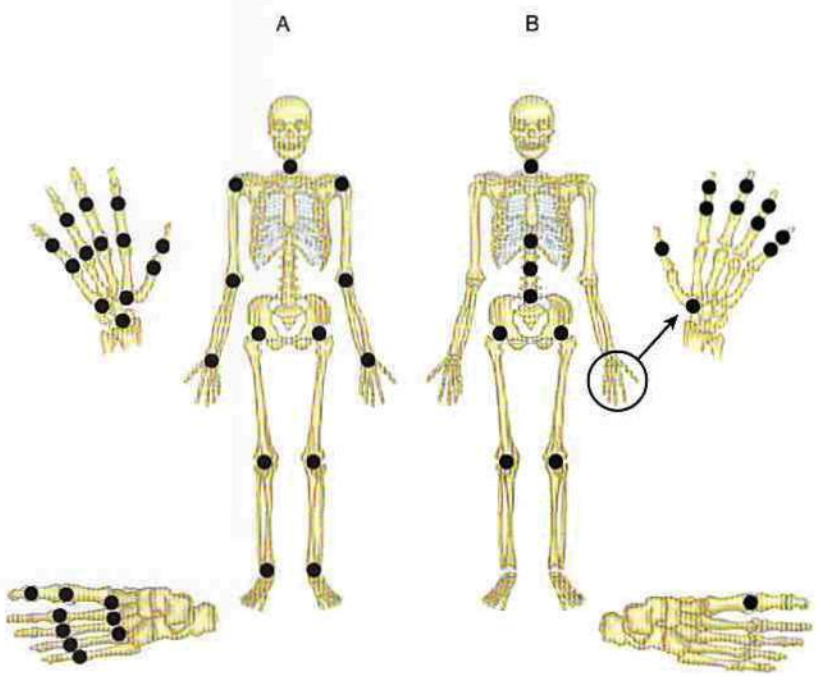


FIGURE 5-24. Distribution of RA and OA. The joint distribution of the two most common types of arthritis are compared: RA (A) and OA (B). RA involves almost all synovial joints in the body. OA has a much more limited distribution. Importantly, RA rarely, if ever, involves the DIP joints, but OA commonly does. (Modified, with permission, from Imboden J, Hellmann DB, Stone JH, *Current Rheumatology Diagnosis & Treatment*, New York: McGraw-Hill, 2004: 162.)

sion by decreasing inflammatory mediators. DMARDs may increase bone healing.

- **Cytokine-neutralizing agents:** Best in combination with DMARD therapy at initial treatment. Anti-TNF antibodies reduce signs, symptoms, and progression.
- **Immunosuppressive and cytotoxic agents:** Leflunomide, azathioprine, cyclosporine, and cyclophosphamide are also effective. Leflunomide is the most commonly used.

Prognosis

RA is highly variable in prognosis, ranging from mild disease with minimal joint injury, to progressive polyarthritis and significant disability. Often, the common clinical characteristics of this disease develop within 1 or 2 years of onset.

Osteomyelitis

Whether acute or chronic, osteomyelitis begins as a phagocytic response leading to osteolysis. In adults, pyogenic bacteria and mycobacteria reach the bone via hematogenous spread (~ 20%), or via direct introduction from trauma or nearby infection. The majority (> 50%) of hematogenously spread cases are caused by *Staphylococcus aureus*, while *Pseudomonas aeruginosa* and *Serratia* species are seen in IV drug users. The most common site of acute osteomyelitis is the vertebral body (a favorite location for TB and brucellosis). Following hematogenous seeding via the vertebral arteries (see Figure 5-25), the infection spreads easily to the vertebral disk and adjacent vertebrae. Diabetes, hemodialysis, and IV drug use all increase the risk of vertebral infection. In contrast, sickle cell patients are known for their susceptibility to *Salmonella* species and *S. aureus* infections within long bones.

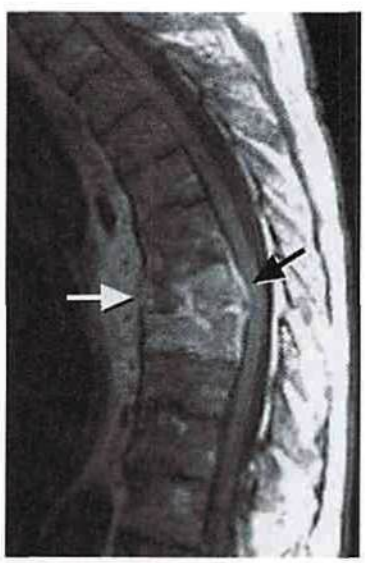


FIGURE 5-25. MRI of vertebral osteomyelitis. Osteomyelitis of the thoracic spine demonstrated on a sagittal, fat-suppressed T1-weighted MRI after the administration of IV gadolinium. At T8–T9, there is involvement of the adjacent vertebral bodies and intervening disk. Abnormally enhancing inflamed tissue extends from the disk space anteriorly (white arrow) as well as posteriorly into the epidural space, compressing the thecal sac (black arrow). (Reproduced, with permission, from Kasper DL, Braunwald E, Fauci A, Hauser SL, Longo DL, Jameson JL, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 747.)

Presentation

In children, acute osteomyelitis is predominantly hematogenous in origin, often accompanied by a history of blunt trauma. When the infection breaks through the periosteum, cutaneous erythema and swelling may be present.

In adults, vertebral infection often presents with neck or back pain, although it may present with abnormal pain in the extremities due to nerve root irritation. These symptoms are accompanied by **low-grade fever** and dull pain that slowly increases over 2 or 3 months. Vertebral percussion elicits tenderness, accompanied by paraspinal muscle spasm. If spinal pain progresses to radicular pain, a spinal epidural abscess should be suspected.

Chronic osteomyelitis is marked by fluctuating activity with periodic exacerbations. Sinus tracts between bone and skin often drain purulent fluid and necrotic bone fragments. Increased pain and ESR accompany exacerbations.

Diagnosis

In addition to these clinical findings, most patients have a normal or only mildly elevated white count. Elevated ESRs (> 100 mm/h) and CRPs are also common. Only 20%–30% of blood cultures will return positive.

Radiographically, early plain films may show soft tissue swelling. At 10 days, a periosteal reaction appears. Lytic changes appear after 2–6 weeks, once 50%–75% of bone density is lost. Within the vertebrae, irregular erosions of adjacent vertebral bodies suggest infection (tumors usually do not extend to adjacent vertebrae). A technetium-99 radionucleotide scan, which is positive in all three phases, is more sensitive in the acute phase. MRI is the best modality for detecting epidural abscesses and should be performed in all suspected cases of vertebral osteomyelitis.

Treatment

Early diagnosis and high-dose antibiotic therapy are essential for preventing bone necrosis. Gram's staining of abscess aspirates should guide the choice of appropriate antibiotic. ESR and CRP levels can be monitored to assess response to treatment.

In children with acute hematogenous infections, oral antibiotics follow 5–10 days of IV antibiotics. In adults, IV treatment for 4–6 weeks should prove effective in both acute hematogenous and vertebral infections. Chronic osteomyelitis can be treated with surgical debridement and long-term antibiotic therapy; however, the risks (including potential limb amputation) can outweigh the benefits. Intermittent antibiotic therapy is effective for suppressing exacerbations.

Osteoporosis

The primary pathology of osteoporosis is a reduction of bone mass in spite of normal bone mineralization. Osteoporosis is defined by the WHO as a reduction in bone mass of ≥ 2.5 standard deviations below the mean for young, healthy, gender- and race-matched controls. This measure, also known as a **T-score**, is clinically useful because it correlates with fracture risk as a sequela of reduced bone density. Two types of osteoporosis are recognized:

- **Type I:** Postmenopausal, secondary to reduced systemic estrogen levels.
- **Type II:** Senile, affecting men and women > 70 years of age.

KEY FACT

T-score classifications:
< 2.5 = Osteoporosis
< 1.0 = Low bone density (osteopenia), with an increased risk for osteoporosis

In women, types I and II are frequently superimposed with increasing age. However, other extrinsic and intrinsic factors may lead to osteoporosis as a secondary outcome, making men susceptible to this condition as well. Osteoporosis affects whites more than blacks or Asians.

Bone density maintenance is a balance between bone deposition (osteoblastic activity) and resorption (osteoclastic activity). These two opposing components of **bone remodeling** serve to repair micro-fractures, maintain skeletal strength, and regulate serum calcium levels. However, any factor favoring resorption over deposition leads to a loss in overall bone mass.

Several key hormones influence the remodeling process:

- **Estrogens:** Deficiency results in increased osteoclast differentiation and activity, leading to increased rates and foci of resorption.
- **Vitamin D:** The active form, 1,25-dihydroxyvitamin D, is produced by coordinated chemical modifications in the skin, liver, and kidney. It increases GI absorption of dietary calcium.
- **Parathyroid hormone (PTH):** PTH increases bone resorption and reduces renal calcium excretion in order to raise serum calcium levels. PTH also causes increased phosphate excretion in the urine.
- **Thyroid hormone:** Hyperthyroidism is associated with increased bone loss.
- **Locally produced growth factors:** These include IGFs, ILs, TGF-β, and PTHrP.

Several extrinsic factors also contribute to the regulation of bone density. Specifically, calcium nutrition and physical activity promote bone deposition, while certain medications (especially glucocorticoids and immunosuppressants) and cigarette smoking hinder this process.

Presentation

Reduced bone density does not produce specific symptoms, therefore osteoporosis may present as a fracture in a patient with reduced bone density. For this reason, the physician's index of suspicion must be elevated, especially in elderly women. According to the National Osteoporosis Foundation, **bone mineral density (BMD)** should be determined in all postmenopausal women with risk factors or all women aged 65 and up. In addition to age and female gender, the intrinsic and extrinsic modifiers of bone remodeling mentioned above should all be considered risk factors. Furthermore, any risk for falls (impaired strength, coordination, or mentation), the most common precipitant of fracture, should be cause for initiation of an osteoporosis work-up.

Older patients who present with sudden-onset back pain may have suffered a vertebral compression fracture (see Figure 5-26). These patients also show loss of height and kyphosis. Hip fractures typically fit a history of a recent fall with pain and weakness in the affected hip and the inability to bear weight. Distal radius (Colles') fractures are also common.

Diagnosis

Dual-energy X-ray absorptiometry (DEXA or DXA) scans have become the most popular method of measuring bone density, although quantitative CT provides helpful information regarding vertebral trabecular bone. Typically, DXA scans of the hip and lumbar spine define clinical BMD measures.

When reduced BMD is found, modifiable risk factors should be sought. Nutritional and hormonal status can be determined by testing serum albumin, calcium, PTH, 25(OH)-vitamin D, and TSH. Bone resorption rates can be

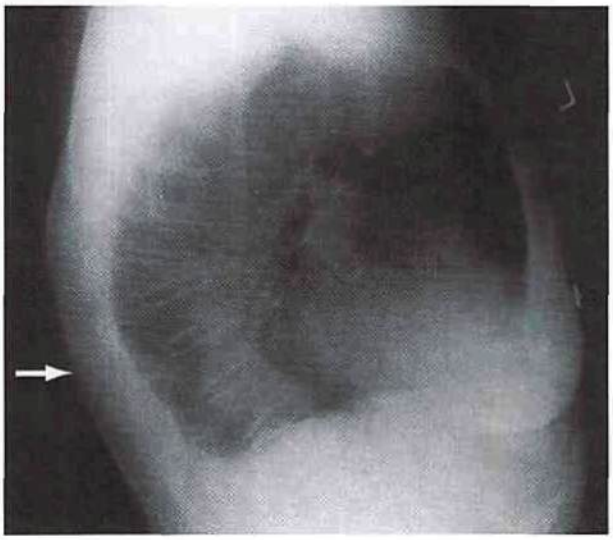


FIGURE 5-26. Vertebral compression fracture. Lateral spine X-ray showing severe osteopenia and a severe wedge-type deformity (severe anterior compression). (Reproduced, with permission, from Kasper DL, Braunwald E, Fauci A, Hauser SL, Longo DL, Jameson JL, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 2269.)

qualitatively determined from serum alkaline phosphatase, urinary hydroxyproline, and 24-hour calcium excretion levels. However, biochemical markers are more useful in monitoring patient response to therapy (when tested at initiation of therapy and 4–6 months later) than in diagnosis.

TREATMENT

When osteoporosis is discovered, a variety of therapies are available. First, calcium and vitamin D deficiencies should be corrected and moderate weight-bearing exercise should be incorporated into the patient's lifestyle when possible.

Estrogen replacement therapies carry increased risks for CVD, stroke, DVT, and breast cancer, and these possible risks must be weighed against the benefits for each individual patient. Alternatively, **selective estrogen receptor modulators** (**SERMs**) are available. These medications (**tamoxifen** and **raloxifene**) have specifically estrogenic effects on bone without the associated risks of hormone replacement.

Bisphosphonates (**alendronate** and **risedronate**) are chemical analogs of pyrophosphate and act to reduce osteoclast number and function. Both are available in daily and once-weekly dosing regimens and lead to fracture risk reduction of 40%–50%. **Calcitonin**, administered intranasally, and PTH both have anabolic effects on bone, thus preventing vertebral fractures. Though PTH reduces vertebral fractures by 65% and nonvertebral fractures by 45%, it is reserved for patients at very high risk for fracture due to a theoretical risk of osteosarcoma with prolonged use.

Specific sequelae are treated as medically indicated. Compression fractures usually require a short course of analgesia. Chronic back pain is usually due to muscle strain and can be treated with relaxation, posture correction, mechanical supports, or muscle relaxants.

Prognosis

Disease progression depends greatly on severity at diagnosis and intensity of intervention. Most patients can do well, though risk increases with age.

Osteopetrosis

Marble bone disease (also known as Albers-Schönberg disease) actually refers to a class of disorders sharing the common feature of defective osteoclastic bone resorption. The infantile (congenital or malignant) form is more severe, arising from an autosomal recessive mutation in the osteoclast cell-surface proton pump. This results in an inability to acidify the ruffled border and a failure of bone resorption. The less severe adult forms (types I and II), also referred to as benign osteopetrosis, are autosomal dominant with varying levels of penetrance. Type II is caused by a mutation in the chloride channel that allows for bicarbonate exchange and continued proton production.

Presentation

The infantile form occurs in 1 in 200,000 to 1 in 500,000 live births. The failure in bone remodeling can lead to cranial nerve paralysis due to foraminal narrowing. Inadequate marrow space can lead to extramedullary and splenic hematopoiesis. The adult forms are typically discovered incidentally by radiography while evaluating a fracture. The prevalence is between 1 in 100,000 and 1 in 500,000. Though referred to as "benign," the adult forms can also present with complications such as deafness, psychomotor deficits, and osteomyelitis.

Diagnosis

Increased thickness of both cortical and trabecular bone leads to typical radiographic changes:

- Thickened cranium and hearing loss.
- Decreased size of paranasal and mastoid sinus cavities.
- Widened diaphyses and metaphyses of long bones.
- Alternating bands of lucency and sclerosis in the iliac crest.

Treatment

The infantile form is best treated with HLA-matched bone marrow transplantation to repopulate functional osteoclast progenitors (of the monocyte lineage). Success rates are highest when performed before the age of 4 years. If left untreated, the infantile form is fatal by the age of 5 years. The adult form, if mild, requires no specific therapy.

Osteomalacia

Calcium and vitamin D deficiencies result in hypocalcemia and hypophosphatemia, leading to impaired bone mineralization. Alternatively, chronic hypophosphatemia due to renal phosphate wasting can also trigger osteomalacia. The key feature is a poorly mineralized bone matrix that is mechanically inferior to normal bone. This can result in bowed extremities, fractures, and proximal myopathy.

KEY FACT

From Latin for bone, "osteo-" and Greek for soft, "malakia."

Presentation

As mentioned above, these patients suffer from increased fractures and bowed long bones.

Diagnosis

A serum 25(OH)-vitamin D level < 15 ng/mL is associated with hypocalcemia and increased serum PTH. The elevated PTH causes increased bone resorption and serum alkaline phosphatase levels. PTH also increases renal calcium reabsorption, leading to phosphaturia and hypophosphatemia, exacerbating the situation.

Radiologically, thinned cortical bone and widespread lucency are apparent. In addition, pseudofractures—radiolucent lines having the appearance of a fracture but lacking clinical signs—are common in the scapula, pelvis, and femoral neck.

Treatment

Vitamin supplementation with 800 IU vitamin D and calcium are integral, though therapy should certainly address the underlying disorder. If renal vitamin D activation is impaired, active forms of vitamin D must be given. If the patient is taking medications that increase vitamin D metabolism or lead to resistance, pharmacologic rescue doses (> 5000 IU for 3–12 weeks) may be required.

Osteitis Fibrosa Cystica

A result of primary hyperparathyroidism, osteitis fibrosa cystica (also known as Recklinghausen's disease of bone) is marked by cystic spaces within the bone, lined by active osteoclasts. These sites of bone resorption often contain disorganized osteoid stroma and old blood, earning them the name "brown tumors." Physiologically, elevated serum PTH levels increase bone turnover, leading to calcium and phosphate release into the blood. PTH acts to increase renal calcium reabsorption and phosphate excretion, leading to accumulation of total body calcium and loss of total phosphorus. PTH also increases vitamin D activation within the kidney.

Presentation

Patients may experience bone pain or tenderness, bowing of bones, and pathologic fractures.

Diagnosis

Serum levels of calcium and alkaline phosphatase are elevated, while phosphorus is decreased. Radiographic examination reveals a ground-glass appearance of cranial bones.

Treatment

The best therapy is to correct the underlying hyperparathyroidism via surgical resection of the parathyroid glands.

Fibrous Dysplasia

Fibrous dysplasia is a sporadic genetic disorder in which expanding lesions composed of mesenchymal cells arise within medullary bone, leading to skeletal abnormalities. In addition, patients may suffer from disordered pigmentation (café-au-lait spots) and endocrine excess (precocious puberty). Together, this triad is known as **McCune-Albright syndrome**. The specific genetic mutation leads to constitutive activation of the $G_s\alpha$ G-protein subunit. This causes autonomous activation of several cellular processes, including bone resorption, pigmentation, thyroid hormone production, and ovarian hormone release.

Presentation

While fibrous dysplasia occurs equally across both genders, the McCune-Albright triad predominates in women (10:1). More frequently, patients suffer only a single skeletal lesion (mono-ostotic form) arising in the third decade. However, patients with multiple lesions (polyostotic form) typically present at < 10 years of age. Early onset generally correlates with greater severity. The polyostotic form afflicts the bones of the face, ribs, proximal femur, and tibia (see Figure 5-27). Expansion of lesions, often exacerbated in the presence of pregnancy or hormonal therapy, leads to pain, deformity, fracture, and possible nerve entrapment.

Diagnosis

Patients presenting with bone pain and café-au-lait spots with rough borders should have plain films of painful regions. Expansile skeletal lesions appear as radiolucent regions with a ground-glass appearance and a thin cortex. Patients may also display symptoms of other endocrinopathies, such as thyrotoxicosis, acromegaly, hyperprolactinemia, hyperparathyroidism, or Cushing's syndrome. Typically, serum alkaline phosphatase may be elevated, but calcium, PTH, and 25(OH)-vitamin D levels are normal.

Treatment

There is no definitive therapy. Surgical intervention is employed to prevent fractures, maintain threatened joints, or decompress nerves. Radiation therapy is ineffective and only increases the low risk of malignant transformation.

KEY FACT

Conditions predisposing patients to gouty arthritis:
Lesch-Nyhan syndrome
Phosphoribosyl pyrophosphate (PRPP) synthetase excess
Decreased uric acid excretion (i.e., renal failure)
Glucose-6-phosphatase deficiency

Gout

Most commonly affecting middle-aged men and postmenopausal women, intra-articular **monosodium urate** (**MSU**) crystal deposition can result in significant arthropathy. Several metabolic abnormalities may underlie this pathology, leading either to increased production or to decreased excretion of uric acid. Dietary excess, physical stressors (e.g., trauma, surgery, or MI), excess alcohol ingestion, and ACTH or glucocorticoid withdrawal can all precipitate an acute attack. Eventually, periodic episodes of acute gout give way to a chronic nonsymmetric synovitis. Gout is also associated with the use of thiazide diuretics because these drugs competitively inhibit the secretion of uric acid.



FIGURE 5-27. Radiograph of polyostotic fibrous dysplasia of the pelvis. (Reproduced, with permission, from Skinner HB, *Current Diagnosis & Treatment in Orthopedics*, 4th ed. New York: McGraw-Hill, 2006: 320.)

Presentation

Acute asymmetrical monarticular joint pain, often of the first metatarsophalangeal joint of the great toe, is the most common presentation. However, polyarticular arthritis may occur in the individuals with concomitant hypertension and alcohol abuse. Classically, acute episodes occur at night, waking patients from sleep to find a warm, red, tender, swollen toe (**podagra**). Early attacks resemble cellulitis, but resolve after 3–10 days. Patients may also present with foci of MSU deposition (**tophi**) in the Achilles tendon or on the external ear.

Diagnosis

Diagnosis must be confirmed by articular fine-needle aspiration and examination for **negatively birefringent needle-shaped crystals** (see Figure 5-28). Synovial white counts are also elevated (~ 60,000 cells/μL). Synovial fluid cultures should be performed if there is a clinical suspicion of simultaneous septic arthritis. A 24-hour urinary uric acid level may also help delineate an underlying metabolic basis. Urinalysis, BUN/Cr, white count, and serum lipids may reveal the presence of serious sequelae of acute gout.

Treatment

Anti-inflammatory medications (**colchicine**, NSAIDs, and intra-articular glucocorticoid injections) are employed during acute episodes for pain relief. Notably, colchicine and NSAIDs can be toxic to the elderly and patients with renal insufficiency or GI disorders. Once acute attacks subside, hypouricemic therapies are used to prevent recurrence. These medications are most effective in patients with hyperuricemia that is refractory to low-purine diets, reduced alcohol intake, and diuretic holidays. **Probenecid** increases uric acid excretion in patients excreting < 600 mg/24 hour or those dependent on thiazide diuretics. **Allopurinol** is best for uric acid overproduction or underexcretion and renal failure.

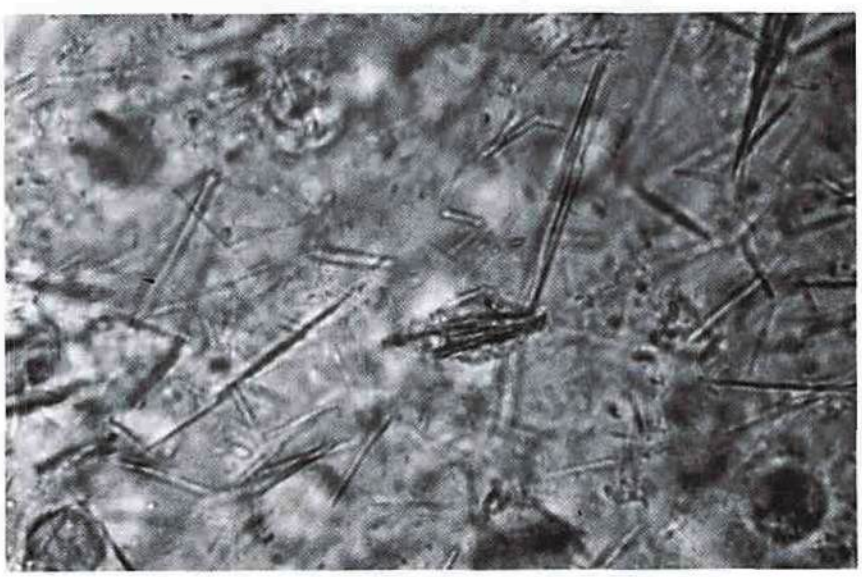


FIGURE 5-28. Monosodium urate crystals. Extracellular and intracellular MSU crystals, as seen in a fresh preparation of synovial fluid, illustrate needle- and rod-shaped strongly negative birefringent crystals (compensated polarized light microscopy; 400 × magnification). (Reproduced, with permission, from Kasper DL, Braunwald E, Fauci A, Hauser SL, Longo DL, Jameson JL, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 2047.)

Pseudogout

Though the underlying mechanism is unclear, **calcium pyrophosphate deposition disease (CPPD)** affects 10%–15% of those 65–75 years of age and up to 60% of those aged 85 and older. Very few CPPD patients have concurrent metabolic abnormalities or a heritable genetic basis. Decreased glycosaminoglycan production may contribute to crystal precipitation. Neutrophil phagocytosis of crystals leads to chemotactic recruitment of more inflammatory cells, as in true gout, perpetuating tissue injury.

Pseudogout occurring in patients < 50 years old should prompt a search for a metabolic basis. Possible culprits include the "four Hs":

- Hyperparathyroidism
- Hemochromatosis
- Hypophosphatasia (low activity of alkaline phosphatase)
- Hypomagnesemia

It is speculated that hyperparathyroidism and hemochromatosis lead to elevated serum calcium and iron, respectively, which inhibit local pyrophosphatases, resulting in increased pyrophosphate crystal precipitation.

Presentation

Though often asymptomatic, many individuals with CPPD suffer from acute and chronic arthritis resembling true gout. However, CPPD can lead to a symmetric proliferative synovitis (more common in familial forms) resembling RA, or intervertebral disk calcification that mimics ankylosing spondylitis. In spite of these peculiar traits, the most common presentation is knee pain, although the wrist, shoulder, elbow, and ankle are also often affected (unlike in OA). Pseudogout attacks may be accompanied by low- to high-grade fevers.

Diagnosis

Once again, joint aspiration leads to definitive diagnosis. Phagocytosed **basophilic, rhomboid crystals with weak positive birefringence** are present. Radiographically, the bony changes mimic other arthropathies; however, the presence of radiodense deposits in menisci or hyaline cartilage (**chondrocalcinosis**) is presumptive evidence of CPPD disease.

Treatment

Colchicine, joint aspiration, NSAIDs, and intra-articular glucocorticoid injections are the mainstays of therapy during acute attacks, sometimes shortening episodes from 1 month to 10 days in duration. Low-dose colchicine prophylaxis aids patients with frequent episodes. Severe polyarticular attacks are best treated with steroids, while progressive large-joint destructive disease requires eventual joint replacement.

CONNECTIVE TISSUE DISORDERS AND VASCULITIDES

Polymyositis and Dermatomyositis

The inflammatory muscle disorders are the most common cause of acquired skeletal muscle weakness, affecting 1 in 100,000 persons. Though polymyositis (PM) is restricted to adults, dermatomyositis (DM) affects both children and adults, and women more often than men. The most dramatic clinical distinction between these two disorders is the **prominent rash that occurs in DM**, though they also differ in their underlying pathophysiology.

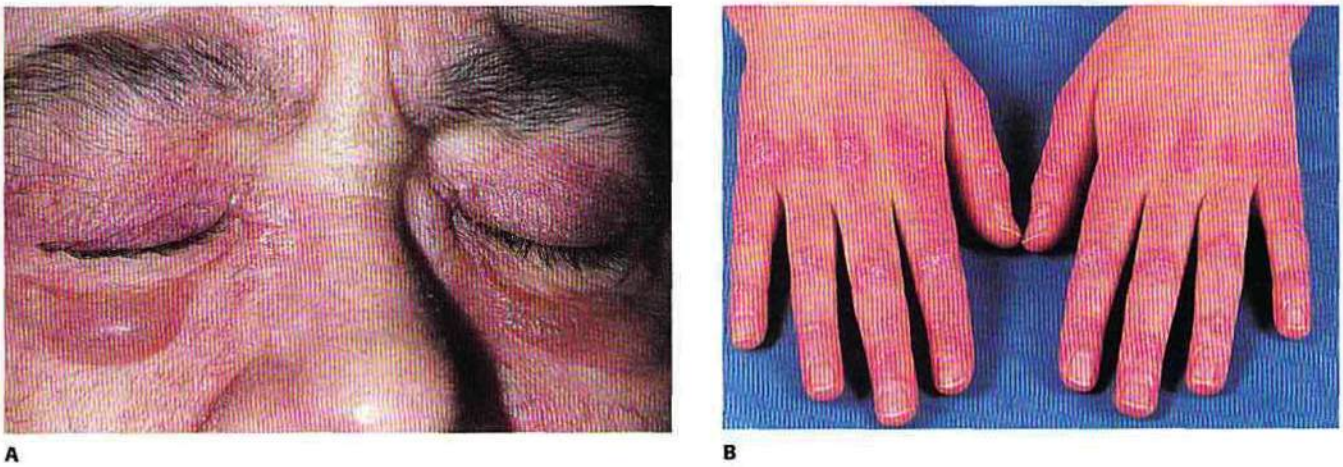
In DM, humoral autoimmunity leads to microangiopathy and muscle fiber ischemia. B-cell infiltrates and complement activation within the thin layer of connective tissue surrounding individual muscle fibers (known as the **endomysium**) contribute to disease progression. In PM, cytotoxic T cells release perforins in response to abnormal muscle cell MHC I expression, leading to muscle necrosis.

PM often mimics other myopathies and is considered a diagnosis of exclusion, occurring in the **absence** of the following symptoms: rash, extraocular or facial muscle weakness, family history of neuromuscular disease, myotoxic drug exposure, muscular dystrophy, neurogenic disorders, endocrinopathy, and muscle enzyme deficiencies. Most commonly it is associated with viral or bacterial infections and autoimmune or connective tissue disorders. Medications such as **D-penicillamine** and **zidovudine** can cause an inflammatory myopathy similar to PM.

The photosensitive rash of DM is heterogeneous, sometimes appearing as puffy, purple eyelids (**heliotrope rash**), as a macular red rash on the face and trunk, or as a purple papular eruption on the knuckles (**Gottron's rash**) (see Figure 5-29). Other areas (knees, back, neck, and shoulders) can be affected as well.

PRESENTATION

Most commonly, the myopathies present with **subacute, symmetrical, proximal, and girdle muscle weakness** that progresses over weeks and months. It is significant enough to inhibit daily activities (rising from a chair, combing one's hair, lifting objects, and climbing stairs). Fine motor movements are affected only late in disease progression and extraocular and facial muscles are spared completely in both syndromes. Pharyngeal and neck muscle involvement do occur, leading to dysphagia and head drop, respectively. Myalgia is rare; if it occurs, a concomitant connective tissue disorder should be suspected.



A B

FIGURE 5-29. Rashes of dermatomyositis. (A) Heliotrope erythema of upper eyelids and edema of the lower lids. (B) Gottron's papules on the dorsa of the hands and fingers, especially over the metacarpophalangeal and interphalangeal joints. (Reproduced, with permission, from Wolff K, Johnson RA, Suurmond D, *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th ed, New York: McGraw-Hill, 2005: 373, 375.)

Diagnosis

Serum muscle enzyme levels aid in diagnosis. **Creatine kinase (CK)** usually parallels disease activity. In addition, electromyography **(EMG)** helps to rule out neurogenic disorders.

Ultimately, however, muscle biopsy provides definitive proof of underlying pathology. PM is a primary inflammatory condition in which T-cell infiltrates are found among healthy muscle fibers, eventually leading to necrosis and phagocytosis. The underlying CD8/MHC lesion is definitive. In DM, endomysial inflammation only occurs in the immediate vicinity of the small vessels. The resulting angiopathy leads to wedge-shaped ischemic injuries within the muscle and peripheral perifascicular atrophy.

Treatment

Immunosuppressant therapy is employed to improve muscle strength and relieve extramuscular symptoms. Plasma CK levels can be followed as evidence of response to treatment, but improvement in muscle strength is the primary endpoint. Patients usually begin on high-dose (1 mg/kg) oral prednisone tapers, with clinical improvement occurring during the third month of therapy. Though most patients respond, up to 75% will require modifications to their treatment regimens due to glucocorticoid side effects, development of steroid resistance, or rapidly progressive disease. Azathioprine, methotrexate, and cyclophosphamide are common second-line agents.

Prognosis

Most patients improve with therapy and achieve full functional recovery through maintenance therapy. PM morbidity usually results from interstitial lung disease, respiratory muscle involvement, or cardiac complications.

Seronegative Spondyloarthropathies

These diseases are characterized by arthritis without RF (no anti-IgG antibody). They occur more commonly in males, and are strongly associated with *HLA-B27*, which is a gene that encodes for **HLA MHC I.**

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is considered a seronegative spondyloarthritis because screening for serum autoantibodies rarely yields positive results. AS onset correlates closely with inheritance of the HLA-B27 haplotype. Ninety percent of patients with AS are HLA-B27 positive.

The underlying cause of AS is unknown; inflamed sacroiliac joints have CD4 and CD8 infiltrates with high levels of TNF-α. The primary site of pathology is the **enthesis**, the site of ligamentous attachment to bone. Inflammation at this site leads to adjacent marrow edema, bony erosions, fibrous progression, and eventual ossification.

Bilateral sacroiliitis is often the earliest manifestation and the hallmark of AS. The sacroiliac joint also shows signs of synovitis and pannus formation. Involvement of the vertebral bodies leads to inflammatory granulation of the anulus fibrosus. Ossification here leads to formation of **syndesmophytes**, which eventually bridge and obliterate the joint space, resulting in the pathomnemonic "**bamboo spine**" seen on radiography. Decreased bone mineral density in the proximal femur and peripheral arthritis are also common.

Presentation

Symptomatic disease onset begins in early adulthood, beginning with insidious deep, dull lumbar or gluteal pain. Morning stiffness that improves with movement, but returns at night and disrupts sleep is also typical. Bony pain at sites of enthesitis may predominate, and is palpable at the major bony prominences of the trunk, girdle, and pelvis.

Several extra-articular symptoms can accompany AS. **Acute unilateral anterior uveitis** occurs in 30% of patients and may precede ankylosis. Up to 60% of patients suffer symptoms of bowel inflammation. **Aortitis, leading to aortic insufficiency** and sometimes precipitating CHF, is a rare but serious extra-articular manifestation of severe and prolonged disease.

At later stages, decreased lumbar range of motion leads to loss of lordosis. Restriction of chest expansion becomes significant. End-stage spinal involvement may result in fracture of brittle, osteoporotic vertebrae, leading to spinal cord injury.

Diagnosis

Definitive diagnosis is clinched with radiographic evidence of sacroiliitis in addition to one of the three following criteria:

- History of inflammatory back pain.
- Limitation of lumbar range of motion (frontal and sagittal planes).
- Limited chest expansion.

Radiographically, sacroiliitis is revealed by blurred cortical margins, bony erosions, and sclerosis. Fibrous progression into joints precedes ossification and appears as "pseudowidening" of the joint space, before joint obliteration by syndesmophytes occurs. Osteitis of anterior vertebral corners leads to "squaring" on plain films and eventual fusion of vertebrae. This fusion appears as a "flat back" deformity (see Figure 5-30). Early changes (bone marrow edema and enthesitis) are best seen on CT or MRI.

No specific laboratory test can clinch the diagnosis of AS. Instead, nonspecific tests are positive, such as elevated serum markers of inflammation (ESR and CRP) in addition to mild anemia of chronic disease.

Treatment

Immunomodulation with anti-TNF-α therapies has revolutionized AS therapy. In several trials, **infliximab** and **etanercept** have demonstrated significant improvement and even resolution of symptoms (morning stiffness, pain, flexibility, and elevated CRP and ESR). In contrast, traditional therapy has included NSAIDs and physical therapy, although these show little effect on disease progression. Uveitis, specifically, is treated with local glucocorticoids. Surgery, in the form of total hip arthroplasty, is reserved for patients with severe hip arthritis, and often results in immediate resolution of pain.

Prognosis

End-stage AS is a chronic progressive disease, significantly reducing patient quality of life. Most patients suffer increasing pain, stiffness, and disability despite traditional therapy.

Reiter's Syndrome and Reactive Arthritis

A triad of **arthritis**, **urethritis**, and **conjunctivitis**. Reiter's syndrome belongs to a larger category of **reactive arthridities (ReAs)** in which up to 85% of suf-

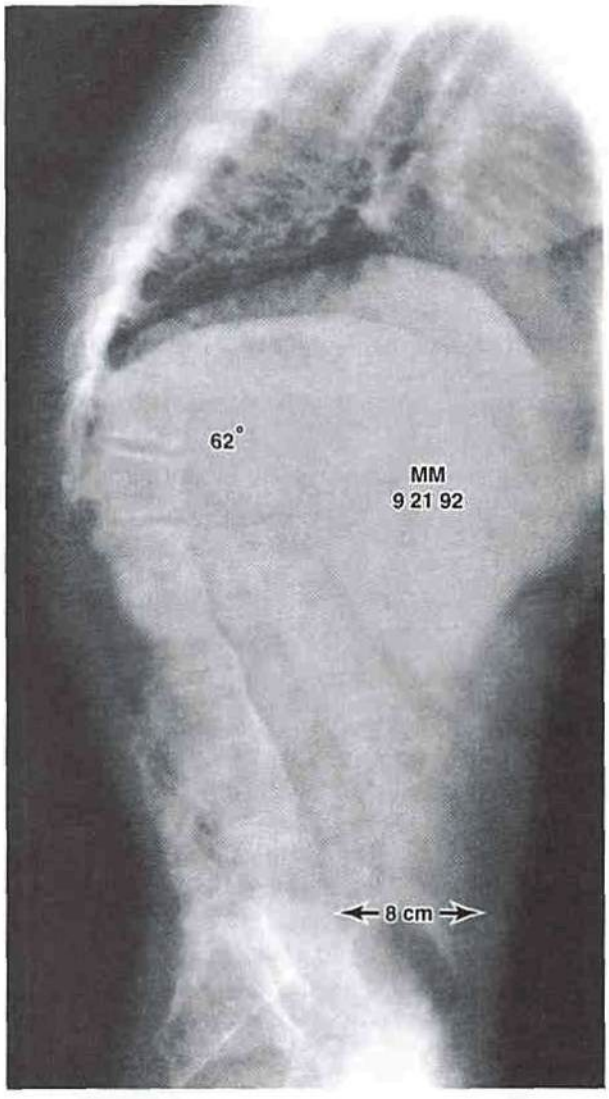


FIGURE 5-30. Radiograph of ankylosing spondylitis. Radiograph demonstrating "flat back" deformity, junctional kyphosis, and sagittal decompensation. (Reproduced, with permission, from Skinner H, *Current Diagnosis & Treatment in Orthopedics*, 4th ed, New York: McGraw-Hill, 2006: 232.)

ferers share the **HLA-B27** antigen. It is thought that patients with this haplotype have a genetic susceptibility to enteric and genital infections that trigger arthritis. In addition, HIV-positive individuals are susceptible to these infections and subsequent ReAs. Several pathogens have been implicated:

- *Shigella*
- *Salmonella*
- *Yersinia*
- *Campylobacter*
- *Chlamydia trachomatis*

MNEMONIC

Can't **see** (uveitis/conjunctivitis).
Can't **pee** (urethritis).
Can't climb a **tree** (arthritis).

Most commonly affecting 18- to 40-year-old males, the pathogenesis is unknown. Each of the inciting pathogens produces **lipopolysaccharide** (**LPS**) and can invade host cells, surviving intracellularly. In addition to similarities in causative pathogens, patients with the B27 haplotype have been found to share a conserved T-cell receptor, which may contribute to the T_H2-mediated inflammation found in ReAs.

Presentation

Usually patients report an antecedent infection less than 1 month prior to the onset of an asymmetric progressive arthritis. Lower extremities (knees, ankles, and feet) are more commonly involved, though wrists and hands are may also be affected. Tense joint effusions, dactylitis, tendinitis, and fasciitis are all common. Associated pathology includes ocular disease, which ranges from conjunctivitis to uveitis, as well as mucosal and ureteral ulcers and sores of the palms and soles.

Diagnosis

As a clinical diagnosis, reactive arthritis should be considered in patients suffering from inflammatory back pain and a spreading arthritis occurring in close temporal proximity to an episode of dysuria or diarrhea. In addition to noting the distribution of joint pain and tendinitis, regions of common extra-articular involvement including eyes, skin, nailbeds, genitals, and mucous membranes should be examined.

Treatment

Acute arthritic symptoms are alleviated to varying degrees by NSAIDs, although immunomodulators such as sulfasalazine and methotrexate may provide additional benefit. Prompt treatment of chlamydial infections may prevent the development of subsequent ReA.

Systemic Lupus Erythematosus

SLE is an autoimmune disease mediated by autoantibodies and immune complexes resulting in inflammation and injury within target organs. The immune complexes target DNA, IgG or IgM, complement proteins, and fibrinogen. This disordered immunity is the result of susceptibility genes, which lead to hyperreactive T and B cells, which then interact with persistent autoantigens. **HLA-DQ** and **HLA-DR** alleles have both been implicated. In particular, **autoantibodies target DNA- and RNA-protein complexes**. Molecularly, pathologic antibodies cause:

- Destruction of Ig-coated circulating cells.
- Activation of the complement cascade.
- Release of chemotactic messengers and destructive enzymes.

Ninety percent of SLE patients are women between the ages of 14 and 45. This disease is most common and most severe in black females.

Presentation

Definitive diagnoses requires the documentation of 4 of 11 criteria over the course of the patients' medical history (specificity and sensitivity: ~ 95% and 75%, respectively) (see Table 5-7). In addition, **antinuclear antibodies** (ANAs) are positive in > 95% of patients; repeated negative results make the diagnosis less likely. Symptoms include fever, fatigue, rash, arthritis, weight loss, nonbacterial verrucous endocarditis, and Raynaud's phenomenon.

With the potential to affect nearly every organ system, SLE sequelae are quite diverse, and include constitutional symptoms such as fatigue and low-grade fever. Descriptions of major organ system manifestations are shown in Table 5-8.

Cutaneous: Lupus dermatitis (see Figure 5-31) can be discoid, systemic, or subacute. Most commonly, this occurs as the photosensitive, raised, erythematous **malar rash** over the cheeks and nose (sparing the nasolabial fold).

TABLE 5-7. Classification Criteria for the Diagnosis of SLE

A patient must have 4 of the following 11 criteria at any time during disease history in order to be diagnosed with SLE	
Malar rash	Fixed erythema, flat or raised, over the malar eminences.
Discoid rash	Erythematous circular raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur.
Photosensitivity	Exposure to ultraviolet light causes rash.
Oral ulcers	Includes oral and nasopharyngeal ulcers, observed by the physician.
Arthritis	Nonerosive arthritis of two or more peripheral joints, with tenderness, swelling, or effusion.
Serositis	Pleuritis or pericarditis documented by ECG, or rub or evidence of effusion.
Renal disorder	Proteinuria > 0.5 g/d or 3+, or cellular casts.
Neurologic disorder	Seizures or psychosis without other causes.
Hematologic disorder	Hemolytic anemia or leukopenia (< 4000/μL), lymphopenia (< 1500/μL), or thrombocytopenia (< 100,000/μL) in the absence of offending drugs.
Immunologic disorder	Anti-ds-DNA, anti-Sm, and/or aPLs.
Antinuclear antibodies	An abnormal titer of ANAs by immunofluorescence or an equivalent assay at any point in time in the absence of drugs known to induce ANAs.

(Data from criteria published by EM Tan et al. *Arthritis Rheum* 21:1271, 1982; updated by MC Hochberg, Arthritis Rheum 40 (9): 1725, 1997. Reproduced, with permission, from Kasper DL et al (eds.) *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 1962.)

The rash can also spread to the ears, chin, neck, and back, and is mediated by immune complex deposition at the dermis-epidermis junction. Subacute cutaneous lupus presents as scaly erythematous plaques resembling psoriasis. Other rashes and oral ulcers also occur.

Musculoskeletal: Most patients experience intermittent polyarthritis, synovitis, and swelling and tenderness in the knees, hands, and wrists. Bony erosions are rare; they are more commonly seen in RA. Persistent pain in any one joint should increase clinical suspicion for **ischemic necrosis**, especially in those patients receiving systemic glucocorticoid therapy. Myalgias are also commonplace, and must be distinguished from steroid side effects.

Renal: Lupus nephritis is a common cause of morbidity in SLE. Every SLE patient should be screened for asymptomatic nephritis with a urinalysis and serum BUN/Cr level. Like other forms of nephritis, classification is histologic

TABLE 5-8. Organ System Manifestations of Systemic Lupus Erythematosus

Organ System	Manifestation	Notes
Cutaneous	Lupus dermatitis	Discoid (DLE), systemic, and subacute cutaneous (SCLE); most commonly a photosensitive, red, scaly **malar rash** over the cheeks and nose.
Musculoskeletal	Polyarthritis and synovitis	Swelling and tenderness in knees, hands, and wrists; bony erosions are more common in RA.
	Myalgias	Must be distinguished from steroid side effects.
Renal	Lupus nephritis	Morbid SLE complication; elevated creatinine, with hematuria and proteinuria.
Nervous	Cognitive dysfunction	Decreased memory and reasoning.
	Headaches	Intensify with SLE flares.
	CNS vasculitis	Very problematic.
	Psychosis	Must be distinguished from steroid side effects.
Pulmonary	Pleuritis	With or without pleural effusion.
	Interstitial inflammation	*Fibrosis is a life-threatening complication.*
Cardiovascular	Accelerated atherosclerosis	Thrombotic and embolic disease leads to increased MI and stroke risks.
	Myocarditis	Can result in arrhythmias.
	Libman-Sacks endocarditis	Leads to valvular insufficiency and embolic CVAs.
Hematologic	Anemia of chronic disease	Normochromic, normocytic.
	Thrombocytopenia	If > 40000/μL, no therapy is needed.
	Leukopenia	Primarily lymphocytopenia.
Gastrointestinal	Vasculitis	Leads to perforations, ischemia, and bleeding.
	Lupus pancreatitis	Very problematic.
Ocular	Sicca syndrome	a.k.a. Sjögren's syndrome.
	Nonspecific conjunctivitis	
	Retinal vasculitis	May be vision-threatening; treated with aggressive steroid therapy.
	Optic neuritis	

(involving deposition of immune complexes within glomeruli and **wire loop** lesions). Dangerous forms of proliferative glomerulonephritis result in hematuria and proteinuria. Most patients with nephritis develop hypertension; 50% progress to a nephrotic syndrome. Ethnic differences in prognosis do exist, with African Americans being more likely than Caucasians to progress to end-stage renal disease.



A B

FIGURE 5-31. Cutaneous manifestations of SLE. (A) Bright red, sharply defined erythema with slight edema and minimal scaling in a "butterfly" pattern on the face in this patient with acute disease. This is the typical malar rash. Note also that the patient is female and young. (B) Well-demarcated, erythematous, hyperkeratotic plaques with atrophy, follicular plugging, and adherent scale on both cheeks. This is the classic presentation of chronic discoid LE. (Reproduced, with permission, from Wolff K, Johnson RA, Suurmond D, *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th ed, New York: McGraw-Hill, 2005: 385 and 389.)

Cardiovascular: Vascular occlusive diseases are increased in lupus, especially in those patients with **anti-phospholipid antibodies (aPL).** These aPLs lead to false-positive results on syphilis RPR/VDRL tests. Accelerated atherosclerosis leads to significant increased risk of stroke and myocardial infarction. Vasculitides also contribute to cerebrovascular events—the presence of aPL and other high scores of disease activity (anti-DNA antibody levels) signal higher risk. Clinicians must pursue risk reduction through aggressive treatment of hypertension and dyslipidemia. Long-term anticoagulation may be indicated in hypercoagulable patients. In addition to vascular manifestations, inflammatory pericarditis is frequently seen. More worrisome, however, are the development of lupus myocarditis and **Libman-Sacks** endocarditis. Valvular disease leads to mitral and aortic valve insufficiency, and sometimes emboli, which also increase stroke risk. When cardiac involvement is discovered, high-dose glucocorticoid therapy is initiated and patients are monitored for serious sequelae (heart failure and arrhythmias).

Gastrointestinal: Nausea, vomiting, and diarrhea can be manifestations of SLE, typically resulting from vascular disease within the abdomen. Vasculitis involving the intestine is a very serious complication, and may result in perforation, ischemia, GI bleeds, diffuse abdominal peritonitis and potentially sepsis. Aggressive high-dose steroids are employed to avoid life-threatening sequelae. Most patients have elevated ALT and AST levels.

Diagnosis

The most important test is for the presence of **ANA**, which is positive in > 95% of SLE sufferers. ANA is very sensitive, but it is not specific for SLE, as ANA can also be elevated in RA, TB, histoplasmosis, and malignant lymphoma. High anti-double-stranded DNA (**anti-ds-DNA**) and **anti-Smith** (anti-Sm) titers are both specific for lupus. Anti-ds-DNA antibodies predict a poor

prognosis. aPL antibodies are not specific, though they fulfill 1 of the 11 criteria for diagnosis and should therefore be tested. **Antihistone antibodies** are found in drug-induced lupus. The presence of **anticardiolipin** and the **lupus anticoagulant** tests are useful in SLE diagnosis, as is the **Russell viper venom test** (**RVVT**), an activated prothrombin test. Women of child-bearing age should receive a screen for anti-Ro antibodies because of a correlation with increased risk of fetal demise in pregnancy, as well as fetal congenital heart block.

Other tests are used to monitor disease progression and response to therapy. These include associated tests of organ function (urinalysis and creatinine), CBC, and hemoglobin. Complement, IL-2, and anti-DNA antibody levels also reveal disease activity.

Treatment

NSAIDs are the front-line therapy for patients with arthritis and myalgias. Dermatitis, arthritis, and fatigue are addressed with antimalarials. In cases of life-threatening conditions such as lupus nephritis, glucocorticoids, and cytotoxic agents are the mainstays of pharmacologic intervention. **High-dose systemic steroids to control acute symptoms** are recommended for short periods of time due to their high rate of serious complications. Steroid tapers are begun as soon as symptom regression permits, although many patients require long-term low-dose therapy. In this instance, patients should be started on regimens to **prevent common sequelae of steroid use** (e.g., glucose intolerance, osteoporosis, and hypertension). Some regimens cease steroid therapy altogether and replacing it with cyclophosphamide or azathioprine.

Prognosis

While most patients experience a range of disease severity with relatively quiescent stretches punctuated by acute exacerbations, complete regression is rare. Disability is a common end-point for SLE patients, whether due to arthritis, pain, fatigue, or end-stage renal disease. Renal failure results in the most morbidity of all SLE complications.

Sarcoidosis

A chronic disorder of waxing and waning course, affecting men and women aged 20–40 years. It is more common in black females. It is characterized by immune-mediated, widespread noncaseating granulomas and elevated serum angiotensin-converting enzyme (ACE) levels. Arising from disordered immune responses of unknown etiology, it is marked by T_H1 lymphocytes accumulating within organs due to one of two possible inciting events:

- The presence of persistent antigens (or self-antigens).
- Decreased efficacy of T-suppressor cells.

Mononuclear phagocytes then infiltrate tissues in response to released IL-2. In the tissue, the phagocytes then differentiate and fuse to produce the multinucleated giant cells that reside in the center of noncaseating granulomas (see Figure 5-32). B cells are recruited to the outer layers of granulomas, where they produce pathologic levels of immunoglobulins via nonspecific activation. If these processes persist for sufficient time periods, fibrosis and functional deficits ensue, leading to patient symptomatology.

Pathology includes epithelial granulomas containing microscopic **Schaumann** (calcium + protein) and **asteroid** (star-shaped within giant cells) **bodies**. The epithelioid giant cells residing within granulomas are believed to pro-

MNEMONIC

I'M DAMN SHARP

Immunoglobulins (anti-ds-DNA, anti-Sm, anti-PL)
Malar rash
Discoid rash
Antinuclear antibodies
Mucositis (oral ulcers)
Neurologic disorders
Serositis (pleuritis, pericarditis, peritonitis)
Hematologic disorders
Arthritis, **A**lopecia
Renal disorders, **R**aynaud's phenomenon
Photosensitivity

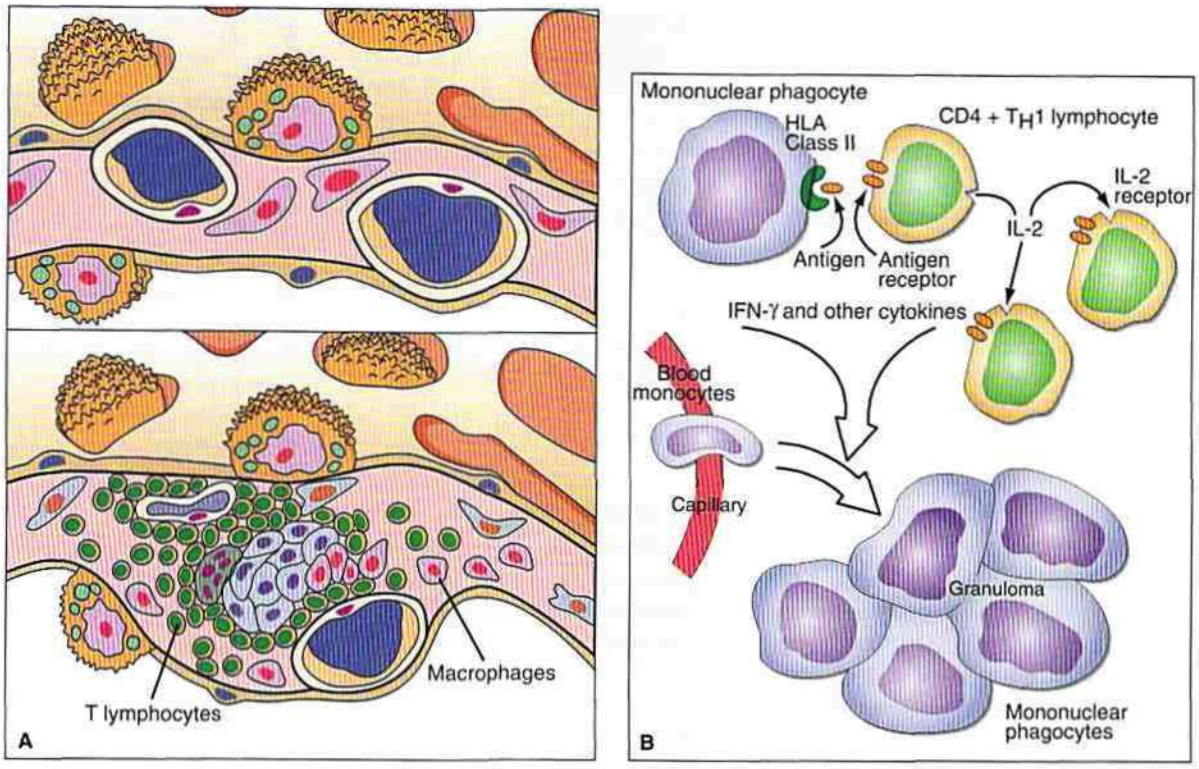


FIGURE 5-32. Pathogenesis of sarcoidosis. (A) Histologic abnormalities. Normal alveoli (top) and alveoli in active sarcoidosis (bottom). The latter are distorted by the accumulated $CD4^+$ T_H1 lymphocytes, alveolar macrophages, and macrophages aggregated into granulomas. There is mild damage to alveolar epithelial and endothelial cells. (B) The exaggerated processes of T_H1 lymphocytes in affected organs result in the accumulation of these cells along with macrophages and macrophages aggregated into granulomas. The trigger for the T_H1 lymphocytes is unknown. The immune response is exaggerated and skewed to produce activated T_H1 lymphocytes that release IL-2, which drives the accumulation of more T lymphocytes. The activated T_H1 lymphocytes also release interferon-γ (IFN-γ). Together with cytokines such as IL-12, macrophage inflammatory protein 1α, and granulocyte-macrophage colony-stimulating factor released in the local milieu, there is recruitment and activation of blood monocytes and subsequent granuloma formation. (Modified, with permission, from Kasper DL, Braunwald E, Fauci A, Hauser SL, Longo DL, Jameson JL, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 2018.)

duce elevated levels of 1,25-dihydroxyvitamin D, leading to enhanced calcium absorption in the gut and hypercalciuria, with or without hypercalcemia.

PRESENTATION

Although sarcoidosis is a systemic disease, the lungs are most commonly affected. Acute or subacute cases develop over short time courses (weeks), presenting with constitutional symptoms of fatigue, low-grade fever, night sweats, malaise, anorexia, and weight loss. Pulmonary symptoms include cough, dyspnea, retrosternal chest discomfort, and hemoptysis. More insidious disease progression may develop over months and cause respiratory symptoms in the absence of constitutional symptoms.

Within the lung, sarcoidosis is primarily an interstitial restrictive lung disease, affecting alveoli, terminal bronchi, and vasculature. Enlarged nodes or altered lung architecture can compress airways leading to distal atelectasis, but typically patients lack signs of wheezing. Instead, auscultation reveals dry rales. Nontender lymphadenopathy is very common, often occurring in the cervical, axillary, tracheal, thoracic, mediastinal/hilar, and inguinal distributions.

About 25% of patients experience skin manifestations, such as **erythema nodosum**, tender deep-seated nodules or plaques on the lower extremities. Other cutaneous manifestations include infiltrated papules about the nose

and erythematous or violaceous papules on the upper extremities (see Figure 5-33). Another 25% suffer eye involvement that can lead to blindness. Typical affected structures include the uvea, iris, ciliary body, and choroids. Posterior uveitis is most common, presenting with blurred vision, lacrimation, and photophobia. Retinal vasculitis and conjunctival involvement may occur. Lacrimal gland inflammation leads to sicca syndrome.

Several other organs can be involved as described in Table 5-9. An acute form, developing over a period of weeks and involving several of these organ systems, has been described. Dubbed the **Heerfordt-Waldenström syndrome**, it occurs as a combination of fever, parotid gland enlargement, anterior uveitis, and facial nerve (or Bell's) palsy

Diagnosis

Sarcoidosis should be considered in any patient between the ages of 20 and 40 who has respiratory complaints, blurry vision, erythema nodosum, and hilar lymphadenopathy. Hilar or mediastinal lymph nodes are known as "potato nodes." Laboratory tests for lymphocytopenia, eosinophilia, increased ESR, hyperglobulinemia, and elevated **ACE** levels all can supplement the diagnosis.

When screening patients for hilar lymphadenopathy, chest films display one of three patterns:

- Type I: Bilateral hilar lymphadenopathy without parenchymal changes.
- Type II: Bilateral hilar lymphadenopathy with diffuse parenchymal changes.
- Type III: Diffuse parenchymal changes without hilar lymphadenopathy.

Patients with type I radiographs tend to have acute but reversible disease, whereas types II and III signal a chronic, progressive form. Pulmonary function tests reveal decreased lung volumes and diffusing capacities. **Gallium-67** lung scans are abnormal, showing diffuse uptake in active areas of inflammation (especially in affected lymph nodes). Other tests are positive for specific types of organ dysfunction.

Treatment

The therapy of choice, as in most inflammatory conditions, is a high-dose glucocorticoid taper. Methotrexate, antimalarials, TNF-α inhibitors, and immu-



A B

FIGURE 5-33. Cutaneous manifestations of sarcoidosis. (A) Brownish-to-purple papules coalescing to irregular plaques, occurring on the face of this man who also had massive pulmonary involvement. (B) Papular brownish to violaceous lesions on the dorsa of a 40-year-old woman who also had pulmonary involvement. Note swelling of the fourth digit of the left hand and of the fifth digit of the right hand. (Reproduced, with permission, from Wolff K, Johnson RA, Suurmond D, *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th ed, New York: McGraw-Hill, 2005: 430 and 431.)

TABLE 5-9. Organ System Involvement in Sarcoidosis

Organ or System	Symptoms	Pathology
Upper respiratory tract	Nasal stuffiness.	Local inflammation.
	Wheezing and stridor.	Obstructive lesions.
Parotid gland	Nontender enlargement.	Space-occupying lesions.
Bone marrow	Anemia, neutropenia, thrombocytopenia.	Marrow infiltration.
Spleen	Splenomegaly.	Space-occupying lesions.
Liver	Elevated LFTs, alkaline phosphatase.	Granulomatous hepatitis.
Kidney	Nephrolithiasis.	Increased Ca^{2+} absorption from granuloma-based vitamin D activation.
Nervous	Seventh nerve palsy.	Local inflammation.
Musculoskeletal	Arthritis of large joints.	Local inflammation.
	Cortical bony lesions of hands and feet.	Space-occupying lesions.
Cardiac	Arrhythmias and heart block.	Local inflammation.

nosuppressants have all been used in refractory cases, though only methotrexate is proven to be effective. Deciding when to treat may prove difficult, as 50% of acute cases spontaneously subside. However, glucocorticoids are known to suppress active disease and should be instituted to protect important organs at risk.

MNEMONIC

GRAIN

Gammaglobulinemia
Rheumatoid arthritis
ACE increase
Interstitial fibrosis
Noncaseating granulomas

Prognosis

Most patients suffering from acute disease achieve remission with no significant long-term sequelae. Half of all patients experience mild permanent organ damage that rarely progresses; 20% are left with intermittent recurring disease and only 10% succumb to direct sequelae of sarcoidosis.

Mixed Connective Tissue Disease

This is an autoimmune disorder with features of lupus, RA, myositis, and progressive systemic sclerosis (SSc). It is generally viewed as one of the less-differentiated connective tissue disorders. The exact pathophysiologic mechanism of mixed connective tissue disease (MCTD) remains unknown. MCTD is 15 times more common in women than in men. It is less common than SLE and about as common as scleroderma.

Presentation

The onset of MCTD is characterized by symptoms seen in scleroderma, SLE, RA, and myositis that occur sequentially. Patients generally present with arth-

ralgias or arthritis, commonly associated with skin changes. Raynaud's phenomenon is seen in 90% of patients, and myositis is present in 75% of patients early in the course of disease. Involvement of the lungs is common in MCTD, although most patients are asymptomatic.

Diagnosis

Major clinical findings include Raynaud's phenomenon, swollen hands, arthritis, esophageal dysmotility, myositis, and pulmonary hypertension, with or without SSc. Most importantly, a high level of anti-U1 ribonucleoprotein autoantibodies (**anti-RNP Ab**) in the absence of the anti-Smith autoantibody (**no anti-Sm Ab**) is required for diagnosis.

Treatment

Generally, SLE-like features, arthritis, and pleuritis are treated with **NSAIDs**, antimalarials (**hydroxychloroquine**), low-dose **corticosteroids**, and methotrexate. Raynaud's is treated symptomatically with calcium channel blockers.

Prognosis

There is a very low incidence of renal involvement with diffuse proliferative glomerulonephritis and neurologic disease. The major cause of mortality is progressive pulmonary hypertension and its cardiac sequelae. The general consensus is that patients with MCTD have a better prognosis than those with SLE.

Systemic Sclerosis

SSc is a systemic disease primarily characterized by skin sclerosis, thickening, and tightening. Also known as scleroderma, it is a heterogeneous disorder both with respect to the involvement of internal organs and joints, and the pace and severity of its clinical course. SSc is most commonly seen in women (female:male ratio of 3:1) between the ages of 35 and 64 years. It is slightly more common in African Americans.

Presentation

In **localized scleroderma**, cutaneous changes consisting of dermal fibrosis are seen without organ involvement. **Diffuse systemic sclerosis** includes fibrotic skin changes with frequent pulmonary, renal, and cardiac involvement. **Limited SSc** presents with fibrotic skin limited to the hands, forearms, feet, neck, and face (see Figure 5-34). Patients may also have Raynaud's phenomenon, telangiectasias, skin calcifications, and late pulmonary hypertension.

KEY FACT

CREST syndrome describes a subgroup of patients with limited SSc, who have **C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactyly, and **T**elangiectasias.

Diagnosis

The major criterion for diagnosis is scleroderma proximal to either the MCP or metatarsophalangeal joints. Minor criteria include sclerodactyly, digital pitting scars, and pulmonary fibrosis. One major and two minor criteria are needed for diagnosis of SSc.

Treatment

No treatment has been shown to be definitively successful in the treatment of scleroderma. Calcium channel blockers are useful in treating Raynaud's phenomenon. Pulmonary hypertension is treated with calcium channel blockers and anticoagulants; in cases of severe pulmonary hypertension, epoprostenol (synthetic prostacyclin) and bosentan (an endothelin receptor antagonist) are used. There is no effective therapy for skin involvement in SSc.

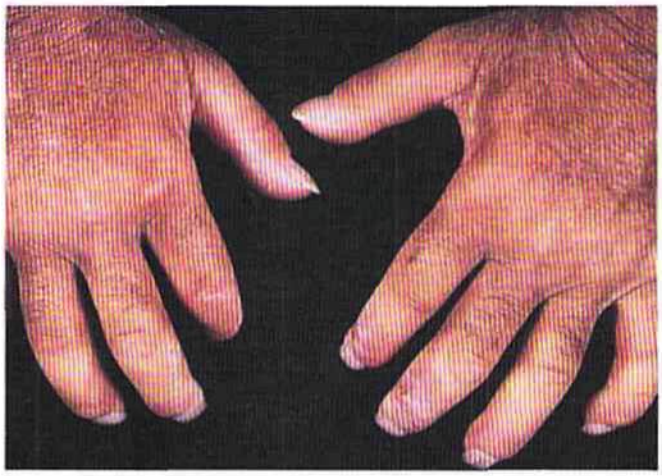


FIGURE 5-34. Scleroderma. Clinical appearance of a patient with scleroderma, displaying typical sclerosis and focal digital ulcers. (Reproduced, with permission, from Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 317.)

Prognosis

The major cause of mortality and morbidity is involvement of internal organ systems, particularly the kidneys and lungs. Though the average survival time following diagnosis is 12 years, this prognosis is strongly affected by the disease subtype. The limited cutaneous form has a much better prognosis than the diffuse cutaneous type. Specifically, renal failure and pulmonary hypertension are the two most common causes of death.

Sjögren's Syndrome

A systemic disease most frequently manifested by dry mouth (**xerostomia**), dry eyes (**xerophthalmia**), and **enlargement of the parotid glands** (see Figure 5-35), resulting from lymphocytic infiltration of these exocrine glands. It affects predominantly middle-aged women, with a 9:1 female:male ratio. Patients are at a 44-fold greater risk of developing non-Hodgkin's B-cell lymphomas than are age-matched controls.

Presentation

The majority of patients complain of dry or painful eyes, also known as xerophthalmia or keratoconjunctivitis sicca (KCS), in addition to xerostomia, and enlargement of the parotid gland. These symptoms are known collectively as **sicca** (dryness) **syndrome**.



FIGURE 5-35. Sjögren's syndrome. Clinical appearance of the enlargement of the parotid gland in Sjögren's syndrome. (Image courtesy of PEIR Digital Library [http://peir.net].)

Diagnosis

The criteria proposed to diagnose Sjögren's syndrome include dry eyes or KCS. Abnormal serologies include positive RF, positive ANA, and/or positive anti-SSA or anti-SS-B.

Treatment

Symptomatic. Artificial tears and saliva preparations can be used to relieve dryness. Cholinergic drugs (i.e., pilocarpine) can increase exocrine secretion. The complications of xerostomia are best prevented by good dental care. Severe extraglandular disease may require high-dose systemic corticosteroids.

Prognosis

Typically very good. Patients have a normal life expectancy. In patients who have associated disorders, the prognosis generally depends on those diseases.

Goodpasture's Syndrome

Goodpasture's syndrome is an autoimmune disorder of unknown etiology, characterized by the triad of diffuse **pulmonary hemorrhage**, **glomerulonephritis** (see Figure 5-36), and anti-glomerular basement membrane (**anti-GBM**) **antibodies.** Anti-GBM antibodies are specifically targeted against type IV collagen, which comprises most of the basement membrane. The disease is associated with **HLA-DR2**; there is a male predominance.

Presentation

Most patients present with hemoptysis, cough, and dyspnea. Fever, chills, nausea, and vomiting are also often present. Renal symptoms may rapidly progress to include azotemia and volume overload. Generally, the disease presents a medical emergency in young men and elderly women.

Diagnosis

Diagnosed by demonstrating circulating anti-GBM antibodies based on suspicion raised by the clinical picture. A lung or renal biopsy may be needed to demonstrate the presence of anti-GBM antibodies in the tissues.

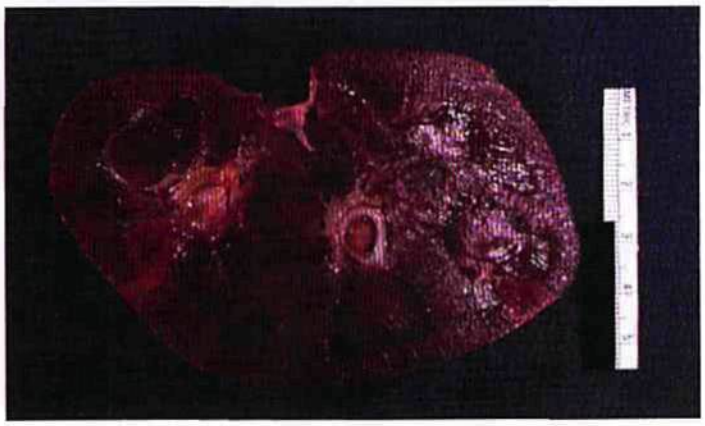


FIGURE 5-36. Goodpasture's syndrome. Gross anatomic appearance of a kidney in Goodpasture's syndrome, showing obvious hemorrhagic glomeruli. (Image courtesy of PEIR Digital Library [http://peir.net].)

Treatment

Aggressive treatment for Goodpasture's syndrome includes corticosteroids, cyclophosphamide, and plasmapheresis in order to remove the circulating anti-GBM antibodies. Patients in acute renal failure may require dialysis.

Prognosis

Presents a medical emergency and the prognosis depends on the progression of the disease. Currently, the 5-year survival rates are about 80%. However, most patients that do survive develop end-stage renal disease, with approximately 30% requiring long-term dialysis.

Giant Cell Arteritis

Giant cell arteritis (GCA), also known as **temporal arteritis,** it is primarily a large-vessel vasculitis, characterized by granulomatous inflammation of the internal elastic lamina. It typically affects the temporal artery, but can involve any of the large branches of the carotids, as well as arteries originating from the aorta. Clinically, it is characterized by temporal tenderness, jaw claudication, proximal muscle pain and stiffness, and occasional ocular changes (see Figure 5-37).

Presentation

Patients usually complain of headaches, typically with scalp tenderness, vision disturbances, jaw claudication, and constitutional symptoms. The disease affects older individuals (rarely less than < 50 years of age). The incidence increases with age, with GCA being almost 10 times more common among patients in their 80s than those in their 50s. It is predominantly reported in white women (female:male ratio of 2:1) of Northern European descent.

Diagnosis

The vast majority of patients present with an ESR > 50 mm/h, making it the most useful laboratory test. The diagnosis is usually based on clinical suspicion and other imaging modalities. Definitive diagnosis requires positive findings on temporal artery biopsy. These typically include the fragmentation of the intima with mononuclear and giant cell infiltrates. Importantly, however, the arteritis may be segmental, so a negative biopsy does not exclude the diagnosis.

Treatment

High-dose prednisone remains the cornerstone of therapy. Treatment usually continues for 6 months and often low-dose prednisone is required for years.

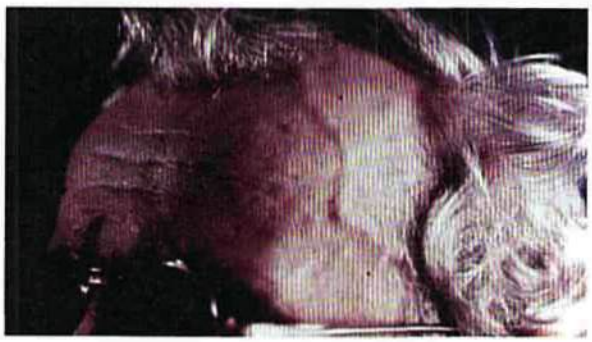


FIGURE 5-37. Temporal (giant cell) arteritis. Clinical appearance of the temporal artery in a patient affected by GCA.(Image courtesy of PEIR Digital Library [http://peir.net].)

Angioplasty is sometimes used in patients not responding adequately to steroid therapy, or those that cannot tolerate it due to side effects.

Prognosis

The most dreaded complication and a major source of morbidity is loss of vision. It occurs in up to 15% of the patients and mostly is due to ischemic optic neuritis. The risk of death appears to be increased within the first 4 months of starting therapy, and is mainly due to vascular complications such as stroke or myocardial infraction.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is characterized by inflammation of small and medium medium-sized arteries, and it typically affects the vessels of skin, peripheral nerves, kidneys, joints, and the GI tract. Histologically, the findings involve a transmural necrotizing inflammation of small- and medium-sized arteries, which can lead to arterial wall weakening and aneurysm formation, causing ischemic changes.

Presentation

PAN is a rare disorder that primarily affects individuals 40–60 years of age. It is more common in males, with a male:female ratio of 2:1. Key clinical features suggestive of PAN include skin lesions (palpable purpura, tender nodular lesions, livedo reticularis, and infarcts of the fingertips), peripheral neuropathy and hypertension with renal sediment abnormalities, and constitutional symptoms. GI involvement due to mesenteric arteritis is seen in 30% of the patients. In males, orchitis is a relatively common symptom.

Diagnosis

Elevated ESR, normocytic anemia, and decreased complement are usually present. Hepatitis B surface antigen is present in 10%–50% of the cases. By definition, antineutrophil cytoplasmic antibodies (ANCA) are absent in PAN. The scoring system used for diagnosis incorporates the presence of symptoms including weight loss, livedo reticularis, myalgias, testicular tenderness, neuropathies, hypertension, and BUN elevation. Definitive diagnosis requires obtaining a biopsy from accessible tissue. The pathologic feature defining classic PAN is a focal segmental necrotizing vasculitis of medium-sized and small arteries (see Figure 5-38).

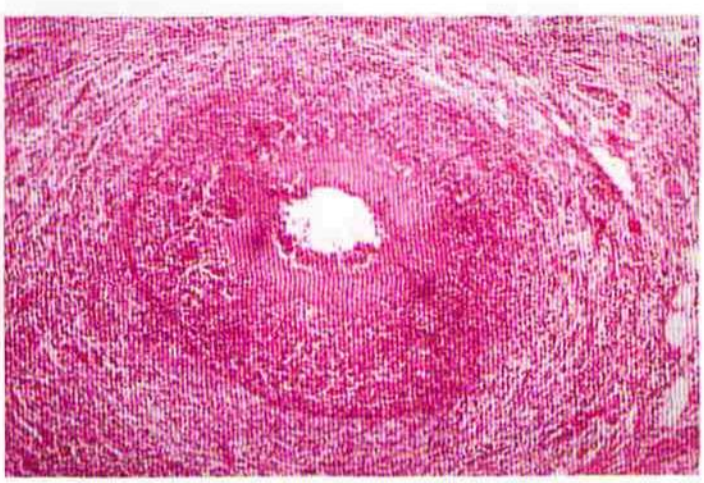


FIGURE 5-38. Polyarteritis nodosa. Histological appearance (H&E stain) of a typical acute lesion of PAN in a medium-sized artery. (Image courtesy of PEIR Digital Library [http://peir.net].)

Treatment

High-dose corticosteroids remain the standard of care. Cytotoxic medications, such as cyclophosphamide, are added to corticosteroids in patients with major organ involvement.

Prognosis

Outcome depends on the presence and extent of visceral and CNS involvement. Most deaths occur within the first year, usually as a result of uncontrolled vasculitis, delay in diagnosis, or complications of treatment. Left untreated, it has a 3-month mortality rate approaching 50%. However, corticosteroid therapy drastically improves the prognosis, raising the 5-year survival rate to about 50% with a single agent, and to 70% with multiple agents.

Buerger's Disease

This is a vasculopathy of small- and medium-sized arteries, characterized by segmental vascular inflammation and the absence of atheromas. Buerger's disease, also known as thromboangiitis obliterans (TAO), is most notable for the fact that it is strongly associated with **heavy tobacco smoking**. It typically affects the extremities. Most people affected are 20–45 years of age, and generally male, but this gender discrepancy is thought to be due to the higher prevalence of smoking among males.

Presentation

Usually presents in younger patients who smoke with distal extremity ischemia, claudication, and pain at rest (see Figure 5-39). Persistent ischemic ulcers of the digits and Raynaud's phenomenon are also commonly present.

Diagnosis

There is no specific laboratory or definitive histologic findings to establish the diagnosis, which is usually based on clinical findings. A scoring system is typically used, which considers the age of the patient (< 45), claudication, superficial vein thrombosis, and Raynaud's phenomenon. To confirm the diagnosis, conditions that mimic TAO must be excluded, the most important among them being atherosclerosis, emboli, autoimmune diseases, hypercoagulable states, and diabetes.



FIGURE 5-39. Buerger's disease. Clinical appearance of the feet in a patient with Buerger's disease, displaying gangrene and toe amputation. (Image courtesy of PEIR Digital Library [http://peir.net].)

Treatment

The only proven treatment for Buerger's disease is the complete discontinuation of tobacco use, which has been shown to prevent disease progression. Treatment of local ischemic ulceration can be attempted with a trial of calcium channel blockers. Limb amputation is sometimes necessary.

Prognosis

There is a stark difference in prognosis for those patients who completely discontinue tobacco use and those who do not. More than 94% of patients who quit smoking avoid amputation, whereas among those that do not, 8-year amputation rate approaches 43%. Of note, even when amputations are not required, claudication and Raynaud's phenomenon often remain present.

Takayasu's Arteritis

Takayasu's arteritis (TA), or **pulseless disease**, is a granulomatous inflammatory vasculitis of large arteries, specifically the aorta and its branches. Its mortality and morbidity arise from the fact that the inflammatory process causes aneurysm formation, stenosis, and thrombosis of large arteries, leading to ischemic changes, such as stroke, TIAs, visual disturbances, and chest and abdominal pain.

Presentation

Patients are typically young women, ranging in age from their teens to thirties. The disease is particularly common in Asian populations. The presenting symptoms are usually constitutional (malaise, fever, and weight loss), and diagnosis is often much delayed. Not uncommonly, the diagnosis is made when a mediastinal mass suspected to be a tumor turns out to be an aortic aneurysm. Up to 10% present without symptoms—the incidental finding of unequal pulses or BPs, bruits, or hypertension prompts further evaluation.

Diagnosis

There are no specific markers for TA. An important diagnostic clinical sign is a BP differential of more than 30 mmHg between the two arms, in addition to asymmetric pulses (despite the synonym for the disease), as well as abdominal bruits and retinal hemorrhages. Arteriography and MRA are imaging modalities commonly used for diagnosing TA. The lesions of TA are most often long-segment stenosis or arterial occlusions of the aorta and visceral vessels at their aortic origin. Due to the involvement of large arteries, biopsies are not performed.

Treatment

The main treatment for TA is high-dose systemic steroid therapy. Methotrexate and cyclophosphamide are used in patients who do not respond to steroid therapy, or as steroid-sparing agents.

Prognosis

Given the chronic relapsing-remitting nature of TA, patients require long periods of steroid treatment, which carry significant risks and side effects. While the overall 15-year survival rate is reported to be as high as 90%, the morbidity and mortality depends on the degree of vascular and organ damage, including aneurysm formation, aortic insufficiency, hypertension, and vision changes. Sudden death occurs as a result of myocardial infarction, stroke, or aneurysmal rupture.

Wegener's Granulomatosis

Wegener's granulomatosis (WG) is a systemic vasculitis characterized by granulomatous involvement of predominantly small-sized vessels and necrosis of the upper and lower respiratory tracts, extravascular granulomatous inflammation, glomerulonephritis, and variable involvement of other organ systems. Granulomatous necrosis may cause tissue destruction, leading to saddle-nose deformity, septal perforation, otitis media, mucosal ulcerations, strawberry gums (i.e., red, inflamed gums), cough, hemoptysis, and dyspnea. Renal involvement is usually asymptomatic until advanced uremia develops—a very poor prognostic sign.

Presentation

WG affects patients of all ages, both sexes, and all races, although it is somewhat more common in Caucasians. Patients usually present with constitutional symptoms, chronic sinusitis, epistaxis, mucosal ulcerations, oral ulcers, and occasionally chronic otitis media. Care must be taken, as the initial presentation is often misinterpreted as allergic or infectious in origin.

Pulmonary manifestations range from completely asymptomatic patients to chronic cough with alveolar hemorrhage and pneumonitis. Renal disease is present in approximately 15% of patients initially, and ultimately affects 50%.

Diagnosis

In addition to clinical findings, diagnosis of WG is established by demonstrating the presence of c-ANCA and anti-proteinase 3 antibodies (98% specificity). In addition, biopsy results are positive for small-vessel vasculitis, focal necrosis, and granulomatous changes.

Treatment

The mainstay of treatment is immunosuppression with high-dose systemic steroids and cyclophosphamide. Additional treatments include methotrexate and trimethoprim-sulfamethoxazole (TMP-SMX) for maintenance therapy to prevent relapse. IV immunoglobulins and plasmapheresis have been used in patients refractory to immunosuppressive therapy and in those with rapidly progressive glomerulonephritis.

Prognosis

When left untreated, WG is a rapidly fatal disease. Mortality is usually caused by renal failure and pulmonary complications, typically within approximately 5 months. However, aggressive immunosuppressive therapy leads to improvement in more than 90% of patients, with about 75% achieving remission. However, due to its relapsing nature, WG still carries an associated 20% mortality rate.

Kawasaki's Disease

A febrile vasculitis of childhood characterized by fever, rash, conjunctivitis, adenopathy, mucocutaneous symptoms, and most notably, coronary artery aneurysms. While its etiology remains unknown, it is likely due to a combination of infectious and autoimmune causes. It is now considered the most common cause of acquired cardiac disease in young children.

Presentation

Diagnosis of Kawasaki's disease (KD) is challenging due to its nonspecific and general presentation. It is a disease of young children with a peak incidence at 9–12 months of age. Children < 2 years of age typically present with sudden-

onset fever that is unresponsive to antibiotics, and they are often found to be disproportionately irritable. Presenting signs also include erythema, desquamation and edema of the extremities, conjunctivitis, rash, lymphadenopathy, strawberry tongue, and swollen, fissured lips (see Figure 5-40). KD is more common in the Japanese population, and slightly more prevalent in males.

Diagnosis

Criteria for the diagnosis of KD include:

- Prolonged high-grade fever.
- Conjunctivitis.
- Cracking and fissuring of lips with inflammation of mucosal membranes (strawberry tongue).
- Cervical lymphadenopathy.
- Rash involving the trunk and extremities.
- Erythema of the hands and feet, progressing to desquamation.

To meet the diagnosis, four of the above criteria, or five with echocardiographic evidence of coronary artery dilatation, must be present.

Treatment

Treatment of KD is aimed at the prevention of cardiac sequelae. IV immunoglobulins and high-dose aspirin are used as anti-inflammatory agents. Anticoagulation with dipyridamole is also considered. For those patients who do develop coronary artery complications, surgical stenting, bypass, and even heart transplantation may be necessary.

Prognosis

While acute KD is self-limiting, the main source of long-term morbidity and mortality is the development of cardiac complications. These include myo-



FIGURE 5-40. Kawasaki's disease. Young patient presenting with cherry-red lips with hemorrhagic fissures, as well as erythema and edema of the fingertips. (Reproduced, with permission, from Wolff K, Johnson RA, Suurmond D, *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed, New York: McGraw-Hill, 2005: 425.)

carditis, pericarditis, congestive heart failure, and aortic insufficiency. Twenty percent of all patients develop coronary artery aneurysms, with a peak incidence in the first 1–2 weeks of illness. Treatment results in significantly better outcomes.

Henoch-Schönlein Purpura

A vasculitis affecting small vessels that is characterized clinically by palpable purpura, colicky abdominal pain, arthritis, and hematuria. While its exact etiology is unknown, histologically it is caused by IgA, C3, and immune complex deposition in arterioles, venules, and capillaries. Henoch-Schönlein purpura (HSP) is a multi-system disease, and tends to involve skin, connective tissues, joints, kidneys, the GI tract, and the scrotum. Importantly, HSP and IgA nephropathy are related disorders, with the key difference being that IgA nephropathy generally only involves the kidneys and affects young adults almost exclusively.

Presentation

Patients with HSP typically present in the spring, fall, or winter. The median age of presentation is 4 years, and the male:female ratio is about 1.5:1. Close to 50% have a history of preceding upper respiratory tract infection. Even when it is not evident on presentation, almost all patients with HSP develop rash and palpable purpura, especially on the lower extremities. Palpable purpura refers to the larger, raised areas of bruising, resulting from extravasation of RBCs outside of vessels, usually indicative of lowered or non-functional platelets. Renal involvement is usually mild. There may be testicular swelling, as well as a history of bloody stools.

Diagnosis

HSP is a clinical diagnosis, as most laboratory values tend to be within normal ranges. Renal tests and urinalysis may be abnormal if the kidneys are involved.

Treatment

Treatment is mainly conservative and symptomatic. NSAIDs are used to relieve joint pain. Even though it does not result in increased purpura, caution must be used in patients with affected kidney function. While no data exist to support their effectiveness, corticosteroids are sometimes used.

Prognosis

Most (97%) children have a self-limited course, lasting 1–2 weeks. However, approximately 20% will have a recurrence during the first year. A small percentage of patients will have persistent purpura, with or without renal involvement. Less than 1% of all cases progress to end-stage renal disease.

Pharmacology

DRUGS USED TO TREAT DISORDERS OF BONE

Bisphosphonates (Risedronate, Alendronate, Clodranate, Etidronate, Pamidronate, Tiludronate, Zoledronate)

Mechanism

Bind to bone, inhibit osteoclast-mediated bone resorption, and also indirectly stimulate osteoblast activity.

Uses

Osteoporosis, Paget's disease, hypercalcemia, metastatic bone disease.

Side Effects

GI disturbances, bone pain, peptic ulcers. Alendronate has been known to cause esophagitis.

Selective Estrogen Receptor Modulators (SERMs) (Raloxifene, Tamoxifen)

Mechanism

Activates estrogen receptors in bone and the cardiovascular system, but has antagonist activity on estrogen receptors in mammary tissue or the uterus. SERMs also inhibit cytokines, recruit osteoclasts, and block PTH's bone-resorbing, calcium-mobilizing action.

Uses

Bone integrity maintenance, osteoporosis prevention, breast cancer.

Side Effects

Hot flashes, postmenopausal vasomotor symptoms, flushing, and increased risk of deep vein thrombosis and pulmonary embolism—tamoxifen is contraindicated where there is history of either. Tamoxifen may increase the risk of endometrial carcinoma via partial agonist effects.

Calcitonin

Mechanism

Inhibits bone resorption. Calcitonin binds to receptors on osteoclasts and inhibits their action. In the kidney, calcitonin decreases the resorption of both calcium and phosphate in the proximal tubules.



MNEMONIC

Calci**tonin** **tones** down serum calcium levels by inhibiting osteoclast action and calcium phosphate resorption.

Uses

Hypercalcemia, neoplasia, Paget's disease, postmenopausal osteoporosis, corticosteroid-induced osteoporosis.

Side Effects

Nausea, vomiting, tingling sensation in the hands, unpleasant taste in the mouth.

Parathyroid Hormone

Mechanism

Stimulates Ca^{2+} absorption in renal distal convoluted tubules and the release of calcium from bone.

Uses

Osteoarthritis

Side Effects

Nausea, headache, dizziness, hypercalcemia, leg cramps.

Etanercept, Infliximab

Mechanism

Block inflammatory cytokine tumor necrosis factor-α; (TNF-α) signaling.

Uses

RA, psoriasis, ankylosing spondylitis, osteoarthritis.

Side Effects

Infection and development of lymphoproliferative diseases.

Cyclooxygenase-2 Inhibitors (Celecoxib, Valdecoxib, Rofecoxib)

Mechanism

Selectively inhibits cyclooxygenase-2 (COX-2) found in inflammatory cells. COX-2 inhibitors spare COX-1, which helps maintain the gastric mucosa and avoids the corrosive effects of nonspecific NSAIDs on the GI lining (see Figure 5-41).

Uses

Analgesic effects for headache, dysmenorrhea, backache, and bony metastases. COX-2 inhibitors are also used for anti-inflammatory effects in chronic or acute inflammatory conditions such as RA and related connective tissue disorders, gout, and soft tissue diseases.

Side Effects

Small but potentially clinically relevant cardiovascular damage.

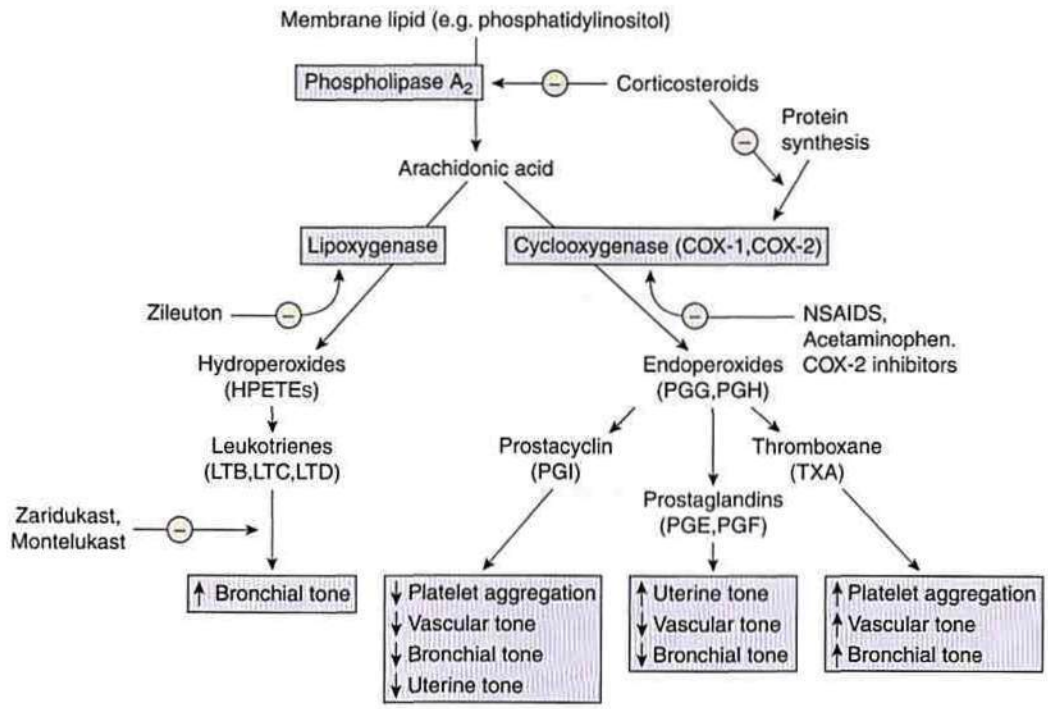


FIGURE 5-41. Mediators derived from arachidonic acid. Summary of mediators derived from arachidonic acid and their actions, and sites of action for anti-inflammatory drugs. (Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination and Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998: 150. Copyright © McGraw-Hill.)

DRUGS USED TO TREAT GOUT

Colchicine

Mechanism

Prevents neutrophil and leukocyte migration into the joint by binding to tubulin, depolymerizes microtubules, and interferes with motility and degranulation (see Figure 5-42).

Uses

Prevention and relief of acute gout attack.

Side Effects

GI disturbances, nausea, vomiting, and abdominal pain. Severe diarrhea may be a problem with large doses, and may be associated with GI hemorrhage and kidney damage. Since indomethacin is less toxic, it is more commonly used.

Allopurinol

Mechanism

Reduces the synthesis of uric acid by inhibiting xanthine oxidase. It is the drug of choice in chronic gout and is ineffective in the treatment of acute gout.

Uses

Long-term treatment of gout.

Side Effects

GI disturbances and allergic skin reactions.

CLINICAL CORRELATION

Allopurinol is also used in lymphoma and leukemia to prevent tumor lysis syndrome and is associated with urate neuropathy.

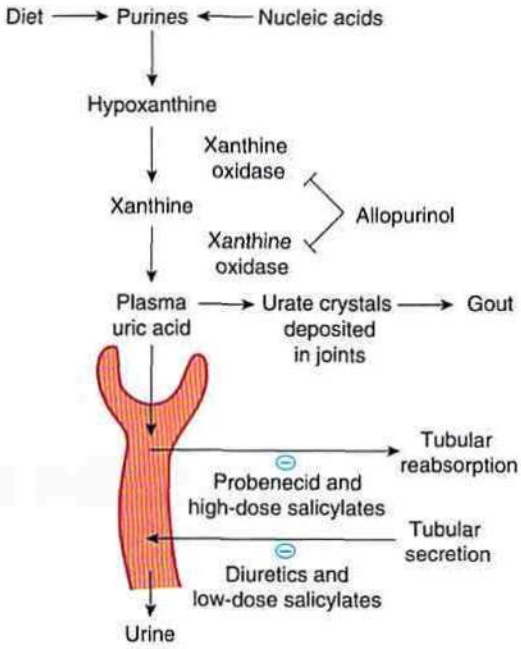


FIGURE 5-42. Pharmacologic interventions in gout.

Probenecid

MECHANISM

Inhibits the absorption of uric acid in the proximal convoluted tubule and increases uric acid excretion. Probenecid has the opposite effect on penicillin secretion and ultimately increases penicillin plasma levels.

MNEMONIC

Probenecid promotes plasma penicillin levels.

USES

Chronic gout.

SIDE EFFECTS

Dyspepsia and peptic ulceration. Hypersensitivity reactions occur occasionally as skin rashes. Drug-induced nephritic syndrome has been reported.

DRUGS USED TO TREAT LUPUS

Corticosteroids

MECHANISM

Enters the nucleus as a steroid-receptor complex to affect protein synthesis. Corticosteroids inhibit production of inflammatory cytokines and relieve mucosal inflammation of asthmatic airways. Corticosteroids reduce bronchial reactivity, increase airway caliber, and reduce the frequency of asthma exacerbations.

USES

Reduction of lupus flare-ups.

SIDE EFFECTS

Puffy face, sleeping difficulties, obesity, diabetes, and osteoporosis.

Cyclophosphamide

MECHANISM

Cross-links DNA and prevents cell replication after the liver metabolizes cyclophosphamide into phosporamide mustard. Cyclophosphamide inhibits T- and B-cell function.

USES

Systemic lupus erythematosus, RA.

SIDE EFFECTS

Ovarian failure, infertility, bone marrow suppression, hemorrhagic cystitis.

DRUGS USED TO TREAT PAIN

Opioids

MECHANISM

Facilitates opening of potassium channels, causing hyperpolarization, inhibiting opening of calcium channels and transmitter release. There are three different types of opioid receptors: μ (morphine), δ (enkephalin), and κ (dynorphin). All opioid receptors are linked through G proteins and inhibition of adenylate cyclase.

Uses

Pain, cough suppression (dextromethorphan), diarrhea (loperamide and diphenoxylate), acute pulmonary edema, and as maintenance for addicts (methadone).

Side Effects

Sedation, respiratory depression, constipation, nausea, miosis (pinpoint pupils), additive CNS depression with other drugs. Opioid antagonists such as naloxone and naltrexone can be given for overdose, as these drugs have little effect on their own but block the effects of opioids. O_2 is contraindicated in morphine overdose, as it might contribute to respiratory failure.

Aspirin

Mechanism

Acetylates and irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) to prevent conversion of arachidonic acid to prostaglandins. Aspirin may increase bleeding but has no effect on PT or PTT.

Uses

Antipyretic, analgesic, anti-inflammatory, antiplatelet activity, OA, and rheumatism.

Side Effects

Gastric ulceration, bleeding, hyperventilation, Reye's syndrome, tinnitus.

Nonsteroidal Anti-Inflammatory Drugs (Ibuprofen, Indomethacin, Ketorolac)

Mechanism

Reversibly inhibits arachidonic acid and cyclooxygenase (COX-1 and COX-2) and inhibits production of prostaglandins and thromboxanes. COX-1 is a constitutive enzyme expressed in most tissues, including platelets. COX-2 is induced in inflammatory cells upon activation. NSAIDs increase bleeding time, but have no effect on PT or PTT.

Uses

Anti-inflammatory, analgesic, antipyretic, and antiplatelet effects. Indomethacin is used to close PDAs.

Side Effects

Renal damage, aplastic anemia, GI distress, ulcers.

Cyclooxygensase-2 Inhibitors (Celecoxib, Valdecoxib)

Mechanism

Selectively inhibits COX-2 and spares COX-1, which helps maintain the gastric mucosa. Thus, COX-2 inhibitors should not have the corrosive effects on the GI lining that COX-1 inhibitors have.

Uses

Rheumatoid and OA.

Side Effects

Similar to those of other NSAIDs; may have less toxicity to the GI mucosa (i.e., lower incidence of ulcers and bleeding). Some studies show an increased risk for cardiovascular problems among certain types of patients.

Acetaminophen

Mechanism

Reversibly inhibits cyclooxygenase, mostly in the CNS, and is peripherally inactivated.

Uses

Antipyretic and analgesic, but lacking anti-inflammatory properties.

Side Effects

Hepatic necrosis because acetaminophen's metabolite depletes glutathione in the liver. Liver damage can be prevented if N-acetylcysteine or methionine is given in time, as they regenerate glutathione.

Rapid Review

Key Terms

Blister	Common Term Used for Vesicle or Bulla
Bulla	Fluid-filled raised lesion greater than 5 mm across.
Excoriation	Traumatic lesion characterized by breakage of the epidermis, causing a raw linear area (i.e., a deep scratch); often self-induced.
Macule	Circumscribed lesion up to 5 mm in diameter characterized by flatness and usually distinguished from surrounding skin by its coloration.
Nodule	Elevated lesion with spherical contour > 5 mm across. **Plaque:** Elevated flat-topped lesion, usually > 5 mm across (may be caused by coalescent papules).
Osteoblastic	Metastatic tumors to bone that are associated with new bone formation (as in prostate cancer).
Osteoid	Newly formed, uncalcified bone matrix synthesized by neoplastic cells.
Osteolytic	Metastatic tumors to bone that are associated with bone destruction (as in breast cancer).
Papule	Elevated dome-shaped or flat-topped lesion ≤ 5 mm across.
Pustule	Discrete, pus-filled, raised lesion.
Scale	Dry, horny, plate-like excrescence; usually the result of imperfect cornification.
Vesicle	Fluid-filled raised lesion ≤ 5 mm across.

CONGENITAL DISEASES

Achondroplasia

An inherited disorder characterized by impaired maturation of cartilage in the developing growth plate. There is a mutation in *FGFR3* causing the gene to be permanently activated, which inhibits cartilage growth. It is the major cause of **dwarfism** (abnormally short stature with underdeveloped limbs). Common presentation of heterozygotes includes shortening of extremities, bowing of legs, and **lordotic posture** (an excessive inward curvature of the spine).

Osteogenesis Imperfecta

A spectrum of disorders with varying severity united by a common feature of abnormal collagen (**type I**) synthesis and resultant bone fragility (brittle bone disease). It is characterized by multiple bone fractures, but can also affect teeth, hearing, and eyes (blue sclerae).

Osteopetrosis (Marble Bone Disease)

A group of uncommon hereditary disorders caused by deficient osteoclastic activity. There is abnormal thickening of the bones which **fracture** easily, causes a shrunken medullary cavity (**anemia** and increased susceptibility to **infections**), and cranial **nerve palsies** (if the bone compresses nerves).

NUTRITIONAL DEFICIENCY

Scurvy

Vitamin C deficiency leading to bone disease in growing children and to hemorrhages and healing defects in both children and adults.

Rickets (Children)/Osteomalacia (Adults)

Vitamin D deficiency leading to hypocalcemia and activation of PTH. This causes loss of bone mass in adults (osteopenia) and bowing of the legs in children.

OSTEOARTHRITIS

Also termed degenerative joint disorder (DJD), this is the most common disorder of the joint and is characterized by degeneration of the articular cartilage. Articular cartilage functions to reduce friction at the joints and evenly distribute weight across the joint surface in weight-bearing bones. It is composed of type II collagen and proteoglycans (decreased in DJD), and is maintained by chondrocytes (decreased in DJD). It usually has a slow onset, presents after age 50, affects the weight-bearing joints and hands, and has the common complaints of joint stiffness, swelling, and pain.

- **Fibrillation:** Early changes in DJD include enlargement and disorganization of chondrocytes at the surface of the articular cartilage, accompanied by matrix changes resulting in fibrillation (splitting).
- **Eburnation:** The fissures begin to extend through the full thickness of cartilage, the cartilage becomes completely eroded, and the underlying bone becomes thickened and polished to an ivory-like consistency (eburnation).

- **Joint mice:** Dislodged bone and cartilage fragments floating in the joint cavity.
- **Subchondral cyst:** Synovial fluid leaks through residual cartilage and underlying bone to form cysts within the bone.
- **Osteophyte:** Bone proliferation at the margins of the joints produces bony excrescences (osteophytes).
- **Heberden's node:** Small osteophytes on the distal interphalangeal (DIP) joints are most often encountered in women with primary OA.

RHEUMATOID ARTHRITIS

RA is a systemic, chronic inflammatory disease affecting multiple tissues but principally attacking the joints. The arthritis typically presents as a symmetric arthritis, mainly affecting the small joints (excluding the DIP joints), may be accompanied by constitutional symptoms, and causes joint pain and stiffness that is worse in the morning. The joint inflammation is immunologically mediated; however, the initiating antigen is not known.

- **Rheumatoid factor (RF):** Circulating IgM autoantibodies directed against the Fc portion of IgG, present in 80% of patients. RF and IgG form immune complexes that fix complement, attract neutrophils, and lead to tissue injury by a type III hypersensitivity reaction.
- **Synovitis:** Affected joints are characterized by synovial cell hyperplasia; perivascular infiltrates of CD4 T cells, plasma cells, and macrophages; angiogenesis; organizing fibrin on the synovial surface in the joint space; and increased osteoclast activity.
- **Pannus:** Focal ulceration of the synovial membrane with proliferation of tissue composed of synovial and inflammatory cells and granulation and fibrous connective tissue that damages the underlying articular cartilage.
- **Rheumatoid subcutaneous nodule:** Firm, nontender masses up to 2 cm in diameter that occur along the extensor surface of the forearm or other areas subjected to pressure. They have a central focus of fibrinoid necrosis surrounded by a palisade of macrophages, which is rimmed by granulation tissue.

Juvenile Rheumatoid Arthritis (JRA)

A group of disorders that cause chronic, idiopathic arthritis in children. RF is usually absent as are rheumatoid nodules. Some variants involve relatively few larger joints such as knees, elbows, and ankles, and are thus called pauciarticular.

OSTEOPOROSIS

A group of skeletal disorders characterized by low bone mass/density, and micro-architectural deterioration with a subsequent increase in bone fragility and fractures. It is caused by an imbalance between bone formation and resorption, with osteoclasts winning out. The most common forms are postmenopausal (estrogen deficiency) and senile osteoporosis. It appears that it is caused by dysregulation of the RANK-RANK ligand-OPG pathway.

- **RANK:** The differentiation of macrophages into osteoclasts requires that RANK ligand (found on the surface of stromal cells or osteoblasts) binds to the RANK receptor on macrophages. Activation of this receptor is a major stimulus in bone resorption. RANK sensitivity is blunted by estrogens.

- **Osteoprotegerin (OPG):** This is a "decoy receptor" produced by stromal cells and osteoblasts that binds RANK ligand without stimulating the formation of osteoclasts. In this way, it regulates the pathway. Production of OPG is stimulated by estrogens.
- **Trabecular bone:** The hallmark of osteoporosis is loss of bone, which is most obvious in parts of the skeleton containing abundant trabecular bone (vertebrae and femoral heads). The bony trabeculae are thinner and more widely separated, which cause increased fragility. The haversian canals are also found to be widened.
- **Dual-energy X-ray absorptiometry (DEXA):** Reliable, early diagnosis of osteoporosis requires radiographic measurements of bone density by techniques such as DEXA.
- **Bisphosphonate and selective estrogen receptor modulators (SERMs):** New therapeutic treatment of osteoporosis includes bisphosphonates (which selectively decrease osteoclast-mediated bone resorption) and SERMs, which have effects similar to those of estrogen without the negative side effects.

PAGET'S DISEASE (OSTEITIS DEFORMANS)

An episodic disease that results in skeletal deformity caused by an accumulation of excessive amounts of abnormal and unstable bone. The causative agent may be a slow **paramyxovirus** infection, which increases expression of the RANK receptor. It affects males more than females, rarely presents before age 40, affects spine, skull, and vertebrae most often, and can lead to **osteogenic sarcoma**. Paget's disease may present as a solitary lesion (**monostotic**) or may be multifocal (**polyostotic**). There are three morphologic phases in Paget's disease:

- **Primary osteolytic phase:** There is focal replacement of the marrow by loose, highly vascular connective tissue. Large osteoclasts line the bony trabeculae and destroy bone.
- **Mixed phase:** Osteoblastic proliferation is superimposed on osteoclastic activity leading to simultaneous bone destruction and formation.
- **Osteosclerotic phase:** Osteoblastic activity ceases but abnormal osteoblastic activity continues. The new bone lacks the lamellar architecture of normal bone and is referred to as **woven bone**.

Mosaic Pattern

New bone formation occurs in an erratic pattern, with areas of new bone juxtaposed in a random mosaic pattern, a virtually **pathognomonic finding of Paget's disease**.

Alkaline Phosphatase

AP is elevated in patients with this disease, reflecting an increase in osteoblastic activity.

Chalkstick Fracture

Transverse fractures of the brittle, weight-bearing long bones have been likened to breakage of chalk, hence the term **chalkstick fracture**.

POLYOSTOTIC FIBROUS DYSPLASIA

Benign, tumor-like lesions that appear to be a developmental defect in bone formation in which the normal trabecular bone is replaced by proliferat-

ing fibrous tissue and disorderly islands of malformed bone. There are three forms:

- **Monostotic fibrous dysplasia (70%):** Involves a single bone, appears during adolescence, and becomes quiescent after bone growth is complete. It is usually asymptomatic.
- **Polystotic fibrous dysplasia (35%):** Involves multiple bones, presents at an earlier age, frequently has craniofacial involvement, and is more likely to have fractures and bone deformity than the monostotic form.
- **McCune-Albright syndrome (3%):** This is polystotic fibrous dysplasia with endocrine abnormalities characterized by unilateral bone lesions, café-au-lait spots, and precocious puberty. It more often affects females.

POLYMYALGIA RHEUMATICA

PMR presents with muscle pain and stiffness in the shoulders and hips, often accompanied by fever, malaise, weight loss, or anemia. There is no muscle weakness. More common in those over age 50. Laboratory exam shows an elevated ESR. Treatment is with steroids, though most cases resolve on their own over a period of years.

- **Temporal arteritis.** Occurs in half of patients with PMR.

DERMATOMYOSITIS

Autoimmune connective tissue disease causing inflammation of the muscles and skin. Presents with progressive proximal muscle weakness causing difficulty with rising from the seated position or raising the arms. Muscle weakness is accompanied by a characteristic dusky red skin rash. Laboratory examination will show elevated CPK and aldolase. Muscle biopsy shows inflammation. Muscle inflammation may affect the heart (detected by ECG). Treatment is with steroids.

- **Polymyositis:** Presents with the same symptoms as DM, without the skin rash.
- **Malignancy:** May be the presenting symptom of an occult cancer.
- **Anti-Jo-1:** Patients may have these autoantibodies.

SJÖGREN'S SYNDROME

Immune disorder defined as a syndrome of dry eyes (xerophthalmia) and dry mouth (xerostomia) affecting females over the age of 40. May also have fever, malaise, and develop dental cavities. Symptoms result from immune response against lacrimal and salivary glands. Diagnosed by salivary gland biopsy, Schirmer test (tests tear production), and presence of autoantibodies. Associated with other autoimmune disorders such as RA and SLE.

- **B-cell lymphoma:** At increased risk.
- **SS-A and SS-B:** Patients may have these autoantibodies.

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is an autoimmune multisystem disease that principally affects the skin, kidneys, serosal membranes, joints, and heart. It is a disease of multifactorial origin, resulting in T- and B-cell activation that culminates in the production of several species of autoantibodies. It affects women more than men and black women more than anyone else.

- **Antinuclear antibodies (ANA):** Directed against several nuclear antigens and can be grouped into four categories: those against DNA, histones, nonhistone protein bound to RNA, and antibodies to nucleolar antigens. They are present in nearly all patients with SLE, but may also be found in other immune diseases.
- **Smith antigen:** Presence of antibodies to double-stranded DNA, or to the so-called Smith (Sm) antigen, is virtually diagnostic of SLE.
- **Lupus anticoagulant:** Phospholipids are required for clotting and patients with antiphospholipid antibodies may display prolongation of in vitro clotting tests such as the PT time; therefore, these antibodies are referred to as lupus anticoagulants.
- **Antiphospholipid antibody syndrome:** Refers to the fact that SLE patients are actually in a prothrombotic state despite the prolonged PT time. They tend to have venous and arterial thromboses, thrombocytopenia, and recurrent spontaneous miscarriages.
- **LE cell:** Phagocytic cell that has engulfed the denatured nucleus of another injured cell. When blood is withdrawn and agitated, a number of WBCs are damaged to expose their nuclei to ANAs, with secondary complement activation; these nuclei are then phagocytized. This "LE test" is present in 70% of SLE patients, but is no longer used.
- **Acute necrotizing vasculitis:** Characterized by necrosis and by fibrinoid deposits within vessel walls containing antibody, DNA, complement, and fibrinogen. In chronic states, this can lead to thickening and luminal narrowing.
- **Photosensitivity:** The skin is involved in the majority of patients and classically manifests as a characteristic erythematous or maculopapular rash over the malar eminences and bridge of the nose (butterfly pattern). Exposure to sunlight makes the rash worse and causes development of a new rash over other exposed areas.
- **Libman-Sacks endocarditis:** Valvular, nonbacterial lesions that take the form of 1- to 3-mm warty deposits, seen on either surface of the leaflets and at the margins.
- **Glomerulonephritis:** Involves deposition of DNA/anti-DNA complexes within the glomeruli. These evoke an inflammatory response that may cause proliferation of the endothelial, mesangial, and/or epithelial cells, and in severe cases, necrosis of the glomeruli.

CRYSTAL ARTHRITIS

Gout

Recurrent episodes of acute arthritis caused by the tissue accumulation of excessive amounts of uric acid (an end product of purine metabolism) due to overproduction or underexcretion. The increased level of uric acid is termed hyperuricemia. Precipitation of MSU crystals from supersaturated synovial fluid activates complement and recruits neutrophils, leading to joint destruction. Gout typically affects men over age 30 and most often (90%) involves the great toe. The arthritis is usually asymmetric, affects only a few joints, and may be accompanied by skin nodules called tophi.

- **Monosodium urate crystals:** Can be identified by examining the synovial fluid. These crystals appear yellow-white and are negatively birefringent.
- **Primary gout (90%):** Gout in which the basic cause is unknown or when the cause is an inborn metabolic abnormality.
- **Secondary gout (10%):** The cause of hyperuricemia is known but gout is not the main or dominant clinical disorder (lymphoma, leukemia, or chronic renal failure). The pathogenesis of gout is related to the overpro-

duction of uric acid resulting from some abnormality in the metabolism of purines.

- **HGPRT:** The conversion of phosphoribosyl pyrophosphate (PRPP) to purine nucleotides is catalyzed by amido phosphoribosyl transferase (PRT) in the de novo pathway, and by adenine PRT (APRT) and HGPRT in the salvage pathway.
- **Lesch-Nyhan syndrome:** An X-linked condition with complete lack of HGPRT leading to excessive amounts of uric acid, mental retardation, and self-mutilation.
- **Chronic tophaceous arthritis:** Recurrent episodes of urate deposition lead to large amounts of chalky white sodium urate (tophi) deposition on articular cartilage, triggering a chronic granulomatous reaction that can lead to ankylosis.
- **Gouty nephropathy:** Uric acid crystals can precipitate within and obstruct renal tubules. Patients undergoing chemotherapy have a rapid cell turnover rate leading to hyperuricemia (tumor lysis syndrome), causing gouty nephropathy.

Pseudogout

Should be included in the differential of arthritis since it is often misdiagnosed as gout or RA or OA. Pseudogout is the result of crystals precipitating out of the synovial fluid. In contrast to gout, these crystals are composed of calcium pyrophosphate. Diagnosis is made by examining synovial fluid and visualization of blue, positively birefringent, crystals. The calcium may also be visualized on X-ray.

ACUTE SUPPURATIVE ARTHRITIS

Infection of the joints may occur during episodes of bacteremia, through traumatic implantation, or from direct spread of an infection from the adjacent bone or soft tissues. It is manifest as local pain, fever, and a neutrophilic joint infiltrate (pus). The immunocompromised, IV drug users, and complement-deficient are at increased risk. Common pathogens include gonococci and *Salmonella*.

GOODPASTURE'S SYNDROME

Glomerulonephritis and hemorrhagic interstitial pneumonitis. Presenting symptoms are hematuria with hemoptysis. Underlying pathology is anti-GBM antibodies that cross-react with the basement membrane of alveoli. The basement membrane antigen is a component of the α-3 chain of type IV collagen.

- **Type I.** Anti-GBM disease characterized by linear deposits of IgG along the GBM. If the IgG also binds to capillary basement membranes of the lung, it is termed Goodpasture's syndrome.

SARCOIDOSIS

Multisystemic disease of unknown etiology characterized by noncaseating granulomas in many tissues and organs. The primary manifestation is bilateral, hilar adenopathy.

- **Schaumann body:** Found inside the granulomas that characterize sarcoidosis. They are laminated concretions composed of calcium and proteins.
- **Asteroid body:** Found inside the granulomas that characterize sarcoidosis. They are stellate inclusions enclosed within giant cells.

- **Lymphangitic distribution:** The granulomas of sarcoidosis predominantly involve the lung interstitium rather than air spaces, with some tendency to localize in the connective tissue around bronchioles and pulmonary venules and in the pleura (lymphangitic distribution).
- **Erythema nodosum:** Hallmark of sarcoidosis. It is characterized by raised, red, tender nodules on the anterior aspects of the legs.
- **Lupus pernio:** Another characteristic skin lesion of sarcoidosis that consists of indurated plaques associated with violaceous discoloration in the region of the nose, cheeks, and lips.
- **Iritis:** Inflammation of the iris.
- **Sicca syndrome:** Ocular lesions that affect the lacrimal glands, with suppression of lacrimation, is called sicca syndrome.
- **Mikulicz's syndrome:** Combined uveoparotid involvement is designated Mikulicz's syndrome.

SERONEGATIVE SPONDYLOARTHROPATHY

Immune-mediated, inflammatory arthritis without serologic evidence of autoimmune disease (absence of RF or ANA). High association with **HLA-B27** (see Table 5-10).

SYSTEMIC SCLEROSIS (SCLERODERMA)

Connective tissue disease causing excess collagen deposition in tissues of the skin, blood vessels, and internal organs. Affects women > men between the ages of 30 and 60. Divided into two syndromes.

- **CREST syndrome:** A more mild form of scleroderma defined as Calcinosis, Raynaud's syndrome (changes in skin coloration on exposure to change in temperature), Esophageal dysmotility (reflux), Sclerodactyly (clawing of the hands), and Telangiectasias.
- **Diffuse scleroderma:** Symptoms of CREST syndrome with additional features of internal organ involvement. More severe and more rapidly progressive.
- **Autoantibodies:** Anti-centromere in CREST syndrome and Anti-Scl-70 in diffuse disease.

TABLE 5-10. Types of Seronegative Spondyloarthropathies

Ankylosing spondylitis	Affects the sacroiliac joints and can progress to involve the spine, hips, and knees. Chronic inflammation prompts new bone growth, leading to fusion of the joints. Symptoms include lower back pain and stiffness with systemic symptoms. Spine X-ray shows characteristic findings.
Reiter's syndrome	Arthritis, conjunctivitis, and urethritis. Arthritis often affects a single joint at the waist or lower. Frequently preceded by GI (*Campylobacter* or *Escherichia coli*) or GU (chlamydial) infection.
Enteropathic arthritis	Arthritis affects 10%–20% of patients with IBD as an extra-GI symptom.
Psoriatic arthritis	Arthritis affects 5%–10% of patients with psoriasis.

SKIN DISORDERS AND DERMATITIS

Atopic Dermatitis

Immune-mediated skin disease causing scaly and vesicular eruptions which rupture and crust over on flexor surfaces. The rash is pruritic. Atopic triad: allergic rhinitis, asthma, and eczema.

Allergic Contact Dermatitis

Delayed-type hypersensitivity reaction to a topical irritant (often poison ivy, cosmetics, or jewelry). The rash appears in a linear distribution mirroring the site of contact with the irritant.

Dermatitis Herpetiformis

Rare disorder characterized by extremely pruritic urticaria and grouped vesicles, mainly along the extensor surfaces. This disease is associated with celiac disease and responds to a gluten-free diet. The IgA antibodies developed against gluten cross-react with reticulin (a component of the anchoring fibrils that tether the epidermal basement membrane to the superficial dermis).

- **Microabscess:** Fibrin and neutrophils accumulate at the tips of dermal papillae, forming microabscesses. Overlying basal cells show vacuolization and minute zones of dermoepidermal separation (microscopic blisters). These zones coalesce to form a true subepidermal blister.

Bullous Pemphigoid

Lesions are tense bullae, filled with clear fluid, on normal or erythematous skin. The bullae do not rupture as easily as the blisters seen in pemphigus, and they usually heal without scarring. It is characterized by a subepidermal, nonacantholytic blister. This is also caused by a type II hypersensitivity reaction, but the autoantibodies are targeting hemidesmosomes.

Pemphigus Vulgaris

Rare autoimmune blistering disorder affecting the mucosa and skin (scalp, face, groin, and trunk). Early lesions appear as superficial vesicles and bullae that easily rupture. Caused by loss of the integrity of normal intercellular attachments within the epidermis and mucosal epithelium. It is caused a type II hypersensitivity reaction. Sera from patients contain pathogenic IgG antibodies to the intercellular cement substance (desmogleins) of skin and mucous membranes (anti-desmoglein IgG).

- **Acantholysis:** Term for dissolution, or lysis, of the intercellular adhesion sites within a squamous epithelial surface. This is common to all forms of pemphigus.
- **Suprabasal acantholytic blister:** In pemphigus vulgaris and vegetans, acantholysis selectively involves the layer of cells immediately above the basal layer, giving rise to suprabasal acantholytic blisters characteristic of pemphigus vulgaris.

Seborrheic Keratosis

A common epidermal tumor that arises spontaneously (mainly on the trunk) and is clinically described as round, flat, coin-like plaques that vary in diameter. The lesions are tan to dark brown (due to melanin pigmentation of basaloid cells) and show a velvety to granular surface. It is benign and easily treated by excision.

- **Horn cyst:** The presence of small keratin-filled cysts (horn cysts) and downgrowths of keratin into the main tumor mass (pseudo-horn cysts) are characteristic features.

ERYTHEMA MULTIFORME

This is an uncommon, self-limited disorder that appears to be a hypersensitivity response to certain infections and drugs. This is probably caused by cytotoxic T-cells targeting cross-reactive antigens in or near the basal cell layer of the skin and mucosae.

- **Stevens-Johnson syndrome:** Symptomatic, febrile version that is marked by erosions and crusting of the mucosal surfaces of the lips, conjunctivae, oral cavity, urethra, and anogenital region.
- **Toxic epidermal necrolysis:** Results in diffuse necrosis and sloughing of cutaneous and mucosal epithelial surfaces, producing a clinical situation analogous to an extensive burn.

LICHEN PLANUS

Pruritic, purple, polygonal papules are the presenting signs of this disorder of skin and mucous membranes. It is usually resolves spontaneously in 1–2 years, often leaving zones of postinflammatory hyperpigmentation. Typically, there are multiple lesions on the extremities, wrists, elbows, or even the glans penis. In 70% of cases, oral lesions are present.

- **Wickham's striae:** Cutaneous lesions of lichen planus consist of itchy, violaceous, flat-topped papules, which may coalesce to form plaques. These papules are often highlighted by white dots or lines, called Wickham's striae.
- **Stratum spinosum:** Histologically, lymphocytes infiltrate along the dermoepidermal junction and are closely associated with basal keratinocytes, which show degeneration, necrosis, and a resemblance in size and contour to more mature cells of the stratum spinosum (squamatization).
- **Dermoepidermal interface:** The inflammation causes this interface to assume an angulated, zigzag contour (sawtoothing).
- **Civatte body:** Anucleate, necrotic basal cells may become incorporated into the inflamed papillary dermis, where they are referred to as colloid, or Civatte bodies.
- **Hypergranulosis:** This disease is differentiated from erythema multiforme because lichen planus exhibits epidermal hyperplasia and thickening of the granular cell layer (hypergranulosis).

SKIN CANCER

Actinic Keratosis

Premalignant (dysplastic) lesions that result from chronic sun exposure, and are associated with a build-up of excess keratin. Lesions are < 1 cm in size and skin-colored with a sandpaper consistency.

- **Cutaneous horn:** Lesions may produce so much keratin that a "cutaneous horn" develops. This is a horn made of keratin protruding from areas frequently exposed to sun.
- **Solar elastosis:** The dermis contains thickened, blue-gray elastic fibers (elastosis), a probable result of abnormal dermal elastic fiber synthesis by sun-damaged fibroblasts.

Squamous Cell Carcinoma (SCC)

The most important tumor arising on sun-exposed sites in older people. Exposure to UV light with unrepaired DNA damage is the most frequent cause, though others exist. Prior to breaking through the basement membrane, SCC appears as a sharply defined, red, scaling plaque. It can become invasive, nodular, develop hyperkeratosis, and may ulcerate. Histologically, atypia is present at all layers of the epidermis. Only 5% metastasize.

- **Dyskeratosis:** Premature keratinization in individual epithelial cells that have not reached the keratinizing surface layer.
- **Xeroderma pigmentosum:** These people cannot repair damaged DNA and rapidly develop skin atrophy (thinning), splotchy pigmentation, telangiectasias, and skin cancers.

Basal Cell Carcinoma

These common, slow growing tumors also arise from chronic sun exposure. Clinically, these tumors present as pearly papules, often containing prominent, dilated subepidermal blood vessels (telangiectasias).

- **Rodent ulcer:** These are advanced lesions that ulcerate with extensive invasion of bone and facial sinuses that occur after many years of neglect.
- **Palisading:** The cells forming the periphery of the tumor cell islands tend to be arranged radially with their long axes in approximately parallel alignment.
- **Separation artifact:** The stroma shrinks away from the epithelial tumor nests, creating clefts or separation artifacts, which assist in differentiating basal cell carcinomas from certain appendage tumors.

Malignant Melanoma

In contrast to nevi, melanomas exhibit striking variations in pigmentation, appearing in shades of black, brown, red, dark blue, and gray. The borders of melanomas are irregular and notched. Clinical warning signs include: a mole that has enlarged, begins itching, or becomes painful; development of newly pigmented lesions in adults; irregular borders; and variegation of color within a pigmented lesion. The most important clinical sign is a change in color or size of a pigmented lesion.

- **Radial growth:** This indicates the initial tendency of a melanoma to grow horizontally within the epidermal and superficial dermal layers. During this time, melanoma cells do not have the ability to metastasize.
- **Vertical growth:** The melanoma now begins to grow downward into the deeper dermal layers as an expansile mass lacking cellular maturation, without any tendency for the cells to become smaller as they descend into the reticular dermis. These cells now have metastatic potential and angiogenesis is stimulated.

PRIMARY BONE TUMORS

Osteoma

These are **benign**, solitary, hard, exophytic growths attached to the surface of bone. They usually affect the head **(paranasal sinuses)** and neck, and are actually developmental aberrations or reactive growths.

Osteoid Osteoma

Benign lesions most often arising in the **proximal femur and tibia** of males (more than females) during the second and third decades of life. They are

less than 2 cm in size and cause pain that can be **relieved by aspirin**. It is composed of haphazardly interconnecting trabeculae of woven bone that are rimmed by prominent osteoblasts. The intertrabecular spaces are filled by vascular loose connective tissue.

Osteoblastoma

Benign lesions most often arising in the **vertebral column** of males (more than females) during the second and third decades of life. They are **greater than 2 cm** in size and cause pain that is **unrelieved by aspirin**. They may **recur** following excision.

- **Nidus:** Osteoblastoma and osteoid osteoma are well-circumscribed lesions with a central area (the **nidus**) that is characteristically radiolucent but may become mineralized and sclerotic.

Giant Cell Tumor of Bone

Neoplasms that consist of two cell types: **multinucleated giant cells** resembling osteoclasts, and neoplastic, proliferating **mononuclear cells**. They cause local pain near joints (mimicking arthritis) in the epiphyses of long bones. There is a slight female predominance with peak age between 20 and 40 years. The lesions are **solitary**, radiolucent, and appear dark brown due to abundant vascularity.

Osteochondroma

Benign proliferations of mature bone with a **cartilaginous cap**. These represent malformations rather than true neoplasms. Most often they are solitary lesions arising from the metaphysis (near the growth plate) of long bones and may cause cosmetic deformities.

Enchondroma

Benign lesions arising from the medullary cavity, composed of mature hyaline cartilage. They occur most often in the small bones of the hands and feet in the third, fourth, or fifth decade of life.

- **Ollier's disease:** Characterized by multiple chondromas involving **one side of the body**.
- **Maffucci's syndrome:** Multiple chondromas associated with benign vascular tumors (**angiomas**) of the soft tissue.

Osteosarcoma

Malignant mesenchymal neoplasms in which the neoplastic cells produce osteoid. They typically present as progressively enlarging, painful masses that come to attention because of fracture of the involved bone. Histologic diagnosis is required in all cases. There are several different forms:

- **Primary vs secondary:** Primary forms arise de novo, while secondary forms arise as a complication of a known underlying process (Paget's disease). Primary osteosarcoma is divided into conventional and variant forms.
- **Conventional vs variant:** The conventional form accounts for three-fourths of cases, most often arises around the knee in the second decade of life, and is seen mostly in males. **Codman's triangle:** This tumor causes an elevation of the periosteum on radiographs, forming Codman's triangle.

Ewing's Sarcoma

Bone tumors that are part of the same "tumor family" characterized by the presence of one of two translocations: **t(11;22)** or **t(21;22)**. The translocations cause dysregulation of cell proliferation and differentiation. These are highly aggressive neoplasms of neural origin (small blue cells histologically), are most common in children, and arise from the medullary cavity in the **diaphysis.** They present with fever, pain, and local inflammation.

- **MIC2 (CD99) antigen:** Ewing's sarcoma cells express this **surface antigen** which can be identified with monoclonal antibody. It is important to distinguish this small blue-cell tumor from others (neuroblastoma), because the treatment is different.

Chondrosarcoma

Malignant neoplasms that arise from the medullary cavity, populated by mesenchymal cells that produce a cartilaginous matrix. They occur more often in **males** during the **sixth decade** of life in the **shoulder, pelvis, proximal femur, or ribs.** Enlarging, painful masses that may metastasize via the blood (to the lung) is the usual presentation. **They do not produce osteoid!**

VASCULITIS

This term simply means inflammation of vessel walls caused by any of the following mechanisms: (1) direct invasion of vascular walls by infectious pathogens, (2) immune-mediated mechanisms, (3) noninfectious, systemic immune-mediated (hypersensitivity or cross-reactivity), or (4) physical or chemical injury (irradiation, trauma, or toxins).

- **Antineutrophil cytoplasmic antibodies (ANCA):** Autoantibodies directed against enzymes within neutrophils, monocytes, and endothelial cells. They are diagnostic for certain disorders and their levels reflect the degree of inflammatory activity.
- **c-ANCA:** Cytoplasmic staining pattern indicating neutrophil granules, and their presence is diagnostic for **Wegener's granulomatosis (WG).**
- **p-ANCA:** Perinuclear staining pattern usually specific for myeloperoxidase(MPO), and their presence is diagnostic for **polyangiitis** and **Churg-Strauss syndrome.**

CHURG-STRAUSS SYNDROME

Vasculitis of small vessels accompanied by granulomas and **eosinophilic necrosis** typically affecting **vessels of the respiratory tract.** There is a strong association with asthma and eosinophilia and **p-ANCA** may be present (~ 50%).

BUERGER'S DISEASE (THROMBOANGIITIS OBLITERANS)

Segmental, thrombosing inflammation of medium- and small-sized arteries of the extremities **(tibial and radial arteries).** The inflammation can extend to adjacent veins and nerves leading to ulcerations of digits and gangrene. It has been associated with heavy cigarette smoking, adults younger than 35, and is more common in Israel, Japan, and India.

TAKAYASU'S ARTERITIS

Granulomatous vasculitis of **medium and large arteries**; however, it is the most common form of systemic vasculitis in **adults under age 50**, with a female preponderance. It can involve ocular disturbances and marked weakening of the pulses in the upper extremities, leading to coldness or numbness in the fingers, ocular disturbances, hypertension, and neurologic deficits.

TEMPORAL ARTERITIS

Acute and chronic, granulomatous inflammation of the **large and small arteries.** It most commonly causes systemic vasculitis in **adults over age 50** and primarily affects the **arteries of the head** (also vertebral and ophthalmic arteries and the aorta), presenting with vague symptoms of fever, headache, and fatigue. Histologically, affected segments of arteries develop nodular thickenings with constricted lumens, granulomatous inflammation of inner media, a mononuclear infiltrate with multinucleate giant cells, and fragmentation of internal elastic lamina.

POLYARTERITIS NODOSA

PAN is a systemic vasculitis of **small- and medium-sized** muscular arteries **(does not involve the arterioles, capillaries, or veins)** affecting the renal and visceral (heart, liver, and GI) vessels most, but typically sparing the pulmonary circuit. Histologically there is transmural inflammation of the arterial wall with neutrophils, eosinophils, and mononuclear cells. Fibrinoid necrosis develops leading to thickening of the vessel wall. PAN frequently follows an episodic course with bewildering symptoms that include fever, malaise, weight loss, hypertension, abdominal pain, bloody stools, and diffuse muscle aches.

WEGENER'S GRANULOMATOSIS

Necrotizing vasculitis affecting small- and medium-sized vessels characterized by a triad of symptoms: (1) acute necrotizing granulomas of the upper and/or lower **respiratory tract**, (2) necrotizing granulomatous vasculitis affecting capillaries, venules, arterioles, and arteries, and (3) renal disease in the form of focal **necrotizing glomerulitis** (often crescentic). **c-ANCA** is present in 95% of patients.

KAWASAKI'S DISEASE

Arteritis involving the **coronary arteries**, usually occurring in children and infants. This disease is the leading cause of acquired heart disease in children of North America and Japan, and is associated with mucocutaneous lymph node syndrome. The vasculitis is PAN-like with necrosis and inflammation affecting the entire vessel wall.

PSORIASIS

Psoriasis is common and frequently affects the skin of the elbows, knees, scalp, lumbosacral areas, and even the glans penis. The most typical lesion is a well-demarcated, pink to salmon-colored plaque covered by loosely adherent scales that are characteristically silver-white. The pathogenesis is unclear, though it seems to be multifactorial (genetic and environmental). The disease results

from sensitized T cells entering the skin, which create an abnormal microenvironment via cytokines.

- **Onycholysis:** Nail changes occur in 30% of patients, including separation of the nail plate from the underlying bed (onycholysis).
- **Pustular psoriasis:** This is a rare variant of psoriasis characterized by formation of multiple small pustules on erythematous plaques. Morphologically, the stratum granulosum is thinned or absent, and extensive overlying parakeratotic scale is seen.
- **Dermal papilla:** Typical of psoriatic plaques is thinning of the epidermal layer that overlies the tips of dermal papillae (suprapapillary plates) and dilated, tortuous blood vessels within these papillae.
- **Auspitz' sign:** The above mentioned blood vessels readily bleed when the scale is peeled back and the suprapapillary plates are "unroofed," giving rise to multiple minute bleeding points. This is Auspitz' sign.
- **Spongiform pustule:** Neutrophils form small aggregates within slightly spongiotic foci of the epidermis (spongiform pustules) and within the parakeratotic stratum corneum (Munro's microabscess).

OSTEOMYELITIS

Denotes inflammation of the bone and marrow cavity by an infectious agent (usually pyogenic bacteria and *Mycobacterium tuberculosis*).

Pyogenic Osteomyelitis

This can be caused by bacterial hematogenous dissemination to bone, direct extension from a focus of acute infection, or traumatic injury/surgery.

- ***Staphylococcus aureus*** is the most common cause of infection.
- ***Escherichia coli*** and **group B *Streptococcus*** are important causes of acute osteomyelitis in neonates.
- ***Salmonella* osteomyelitis** is frequent in patients with sickle cell disease.

Acute Osteomyelitis

An intense, neutrophilic inflammatory infiltrate at the site of bacterial invasion. The vascular channels are compressed and the bone becomes necrotic within days. In children, the **metaphyses** of long bones are typically involved (due to sluggish blood flow).

- **Periosteum:** In long bones, infection can spread through the cortical bone and penetrate the **periosteum.** Subperiosteal abscesses may form (particularly common in children).
- **Epiphysis:** In infants, loosely attached periosteum and anastomoses between metaphyseal and epiphyseal vessels allows infection to spread to the epiphyses, then the joint capsule.

Chronic Osteomyelitis

Sequela of acute infection characterized by osteoclast activation, fibroblastic proliferation, and new bone formation. Residual necrotic bone **(sequestrum)** may be resorbed by osteoclasts. Large sequestra are surrounded by a rim of reactive bone **(involucrum).** When a well-defined rim of sclerotic bone surrounds a residual abscess, it is called **Brodie's abscess.**

URTICARIA (HIVES)

This is a common disorder characterized by localized mast cell degranulation and resultant dermal microvascular hyperpermeability, culminating in pruritic, edematous plaques called wheals. Edema is limited to the perivascular spaces of the superficial dermis. Urticaria usually results from antigen-induced (e.g., pollens and foods) release of vasoactive mediators from mast cell granules via sensitization with specific IgE antibodies (type I hypersensitivity).

- **Hereditary angioneurotic edema:** Result of an inherited deficiency of C1 esterase inhibitor that results in uncontrolled activation of the early components of the complement cascade.

NOTES

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KEY FACT

By week 3, there are three layers of embryonic tissue: the ectoderm, the mesoderm, and the endoderm.

Embryology

NERVOUS SYSTEM DEVELOPMENT

The nervous system is one of the first systems to develop. In the third gestational week, following gastrulation, the neural tube (which will become the central nervous system [CNS]) forms and neural crest cells (which will give rise to the peripheral nervous system [PNS]) emerge and migrate.

Gastrulation

During week 3 of embryogenesis, the three layers of embryonic tissue form through a process known as gastrulation (see Figure 6-1):

- Gastrulation: Ectodermal cells detach from the epiblast, the surface layer of the embryo, invaginate inward into a groove known as the primitive streak, and form the mesoderm.
- Mesodermal cells in the primitive streak then migrate toward the head until blocked by the fused buccopharyngeal membrane at the primitive node (the most rostral part of primitive streak).
- In parallel, prenotochordal cells also invaginate and move rostrally, forming a line known as the **notochord** from the primitive node to the prechordal plate.

KEY FACT

Remnants of the primitive streak can become sacrococcygeal teratomas.

Neurulation

The primitive streak regresses and disappears, dragging the notochord toward the buccopharyngeal membrane.

KEY FACT

The **notochord** becomes the nucleus pulposus, which lies within the vertebral column in the adult. Herniation of the nucleus pulposus through the annulus fibrosis results in spinal root impingement and pain.

The steps of neurulation are summarized in Figure 6-2.

1. The notochord induces the overlying region of the ectoderm to form the **neural plate.**
2. The neural plate begins to invaginate along the longitudinal axis and forms the **neural groove.**
3. The neural groove continues to invaginate until the surrounding neural folds meet to form an open **neural tube.**
4. The open neural tube then closes, starting in the center (at the middle of the future body) and progressing caudally and rostrally.

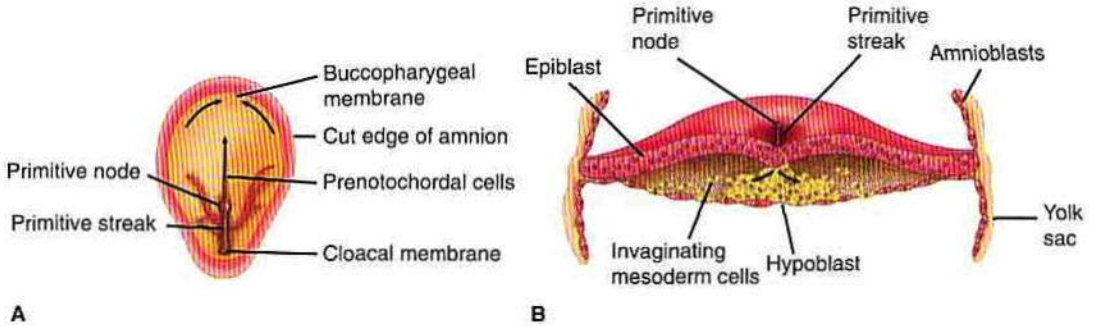


FIGURE 6-1. Gastrulation. (A) Topographical view of migrating cells during gastrulation. Invaginating mesoderm cells (prenotochordal cells) detach from the epiblast and migrate along the longitudinal axis to form the notochord. (B) Cross-sectional view of mesodermal cells detaching from the epiblast.

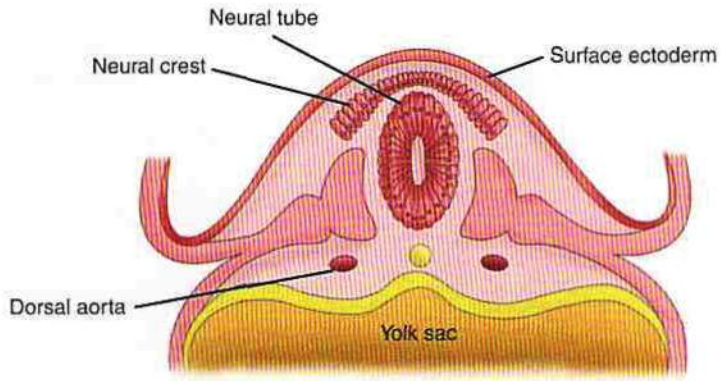


FIGURE 6-2. Neurulation. The neural groove invaginates and closes to form the neural tube.

Neural Tube Defects

Failure of the neural tube to close at either end leads to birth defects.

- Failure of rostral neuropore closure leads to anencephaly.
- Failure of caudal neuropore closure leads to spina bifida (see Figure 6-3).
- Failure of the neural folds to form the neural tube leads to **rachischisis**, with exposed neural tissue. This most extreme form of spina bifida carries a poor prognosis.
- **Cranioschisis** is failure of closure of the neural tube at the cranial end, with lack of brain formation (**anencephaly**).
  - Occurs in 1 in 1500 births.
  - Death occurs within a few days after birth.

Variations of Spina Bifida

The clinical manifestations and severity of spina bifida vary depending on the degree of closure of the caudal/rostral neuropore as well as the location of the defective fusion. Prognosis varies from a completely normal life span (spina bifida occulta) to death within a few years (rachischisis) (see Tables 6-1 and 6-2).

KEY FACT

As a result of the tethering of the spinal cord to the vertebral column, meningocele is often associated with hydrocephaly. As infants grow, the vertebral column lengthens faster than the spinal cord. The vertebral column then pulls the spinal cord and cerebellum downward, occluding CSF flow through the foramen magnum.

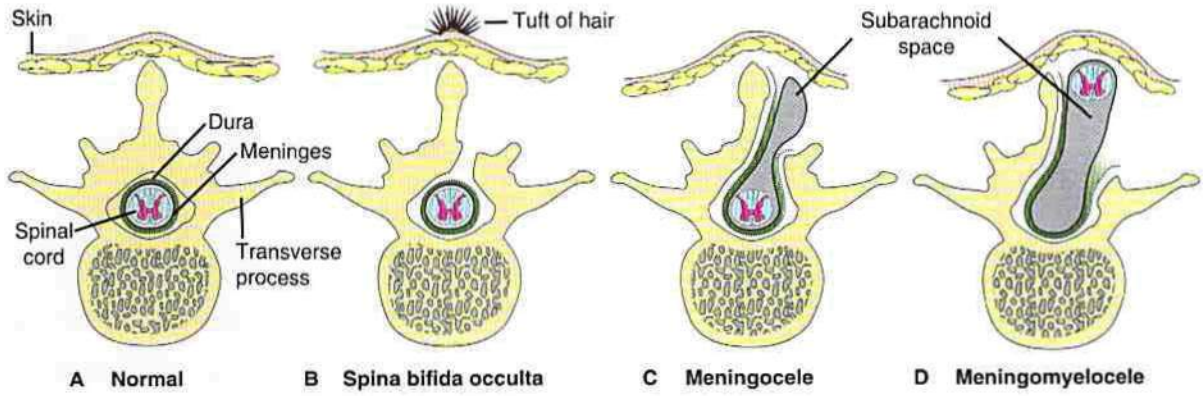


FIGURE 6-3. Types of spina bifida. (A–D) Variations of spina bifida can occur in the ways shown here.

TABLE 6-1. Variations of Spina Bifida

Spina Bifida Occulta	Spina Bifida Cystica	Anencephaly Cranioschisis	Rachischisis
Failure of vertebral arches to close without herniation of intraspinal contents.	Includes meningoceles: Failure of vertebral arches to close with herniation of intraspinal contents.	Not technically a form of spina bifida, but a similar concept: Failure of closure of the neural tube at the cranial end.	Failed neural tube closure.
No defects except for a small tuft of hair overlying a defect in the bony aspects of the spine.		Exposed brain matter.	Neural tissue exposed to the external world; the most extreme form of spina bifida.
Normal life span; 1 in 10 live births.	1 in 1500 birth.	Prognosis is poor, with death a few days after birth.	Poor prognosis.

Cross-Section of the Neural Tube

- The **neural tube** gives rise to the CNS, including the brain, brain stem, and spinal cord.
  - The brain's three primary vesicles develop around week 6.
  - In the brain stem and spinal cord, the dorsal alar plate, the ventral basal plate, and the intervening sulcus limitans develop within the central canal of the neural tube.
    - **Alar plate:** Gives rise to sensory neurons.
    - **Basal plate:** Gives rise to motor neurons.
    - **Sulcus limitans:** Separates the two plates.
- **Neural crest cells** are derived from ectodermal cells. Ectoderm at the edges of the neural folds is induced by the neural tube to form neuroepithelia. These neural crest cells then migrate and give rise to multiple adult derivatives (see Figure 6-4), including:
  - PNS ganglia and neurons.
  - **Schwann** cells.
  - Chromaffin cells of the adrenal medulla.
  - Melanocytes in the skin.
  - Connective tissue and skeletal tissue of the **pharyngeal arches.**
  - C cells of the thyroid.
  - Aortic arch and conotruncal cells.
  - Enterochromaffin cells of the intestines.

MNEMONIC

GAMES:

Glia
Arachnoid/**A**drenal medulla
Melanocytes
Enteric ganglia
Schwann cells

The most common disorders of neural crest cell migration include those listed in Table 6-3.

TABLE 6-2. Variations of Meningocele

Meningocele	Meningomyelocele	Meningoencephalocele	Meningohydroencephalocele
Herniation of the subarachnoid space out into the defect.	Herniation of the spinal cord into the outpouching of the subarachnoid space; **myelo = neurons/cord.**	Same as meningomyelocele except involving the brain instead of spinal cord; brain matter is displaced into an outpouching of the subarachnoid space; **encephal = brain.**	More severe, herniation includes a ventricle with CSF along with the brain matter; **hydro = CSF.**
Neurologic defects but **not** mental retardation.	Associated with type II Arnold-Chiari syndrome.	Mental retardation.	Mental retardation.

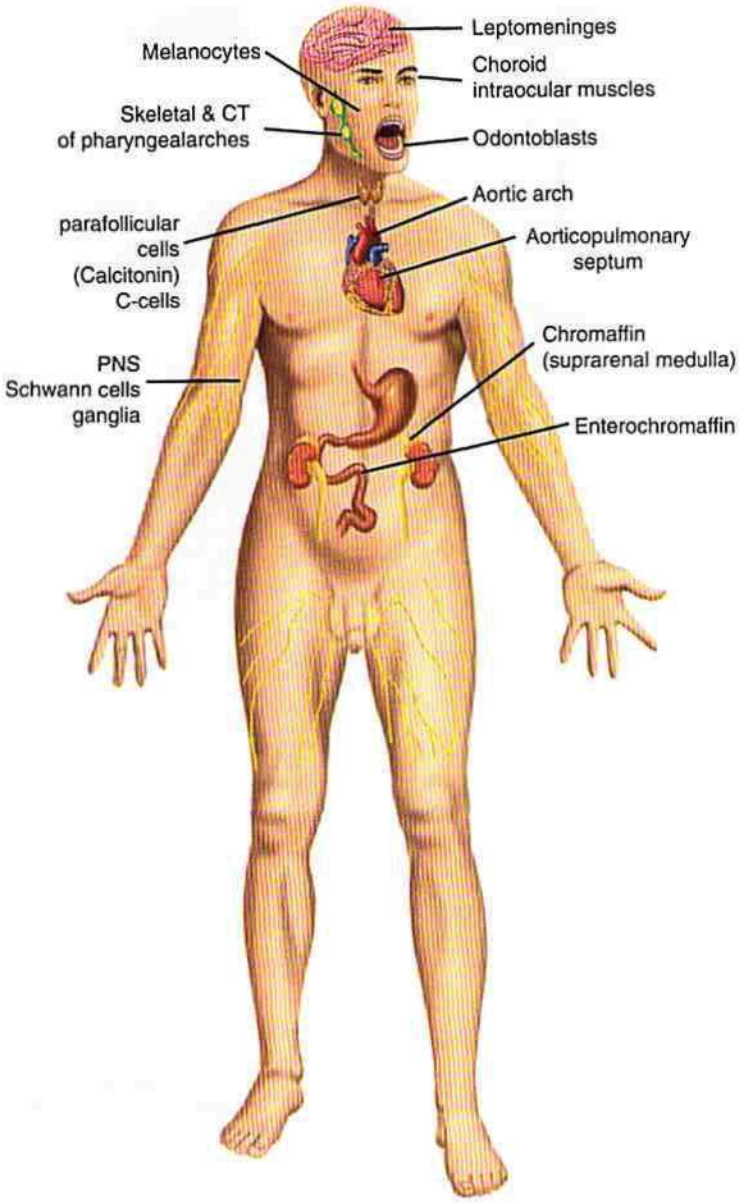


FIGURE 6-4. Neural crest derivatives. The neural crest cells migrate peripherally from the neural tube to develop into the peripheral nervous system and other important structures.

TABLE 6-3. Neural Crest Derivatives and Their Corresponding Defects

Neural Crest Derivative	Defect
Aortic arch/aorticopulmonary septum.	Great vessel deformities.
Pharyngeal arch 3.	DiGeorge's syndrome.
Enterochromaffin cells.	Hirschsprung's disease, achalasia.
Melanocytes.	Albinism.

BRAIN DEVELOPMENT

Formation of Brain Vesicles

From week 6 onward, three primary vesicles form at the caudal end and develop into five secondary vesicles. These secondary vesicles give rise to the mature structures in the adult brain and the associated vesicles/CSF-filled cavities (see Figure 6-5). The three primary vesicles are:

- Forebrain (prosencephalon).
- Midbrain (mesencephalon).
- Hindbrain (rhombencephalon).

The five secondary vesicles are:

- Telencephalon (derived from the prosencephalon).
- Diencephalon (derived from the prosencephalon).
- Mesencephalon.
- Metencephalon (derived from the rhombencephalon).
- Myelencephalon (derived from the rhombencephalon).

Congenital Malformations

Arnold-Chiari

Arnold-Chiari syndrome is congenital herniation of the cerebellum through the foramen magnum (see Figures 6-6 and 6-7).

KEY FACT

Syringomyelia = fluid-filled cavity (cyst) within the spinal cord.

- Occurs in 1 in 1000 live births.
- Type I: Herniation of cerebellar tonsils only.
- Type II: Breaking of the tectal plate, aqueductal stenosis, herniation and unrolling of the vermis into the vertebral canal, and stretching of CN IX, X, and XI. May also present with syringomyelia in C8–T1 and lumbar meningomyelocele.

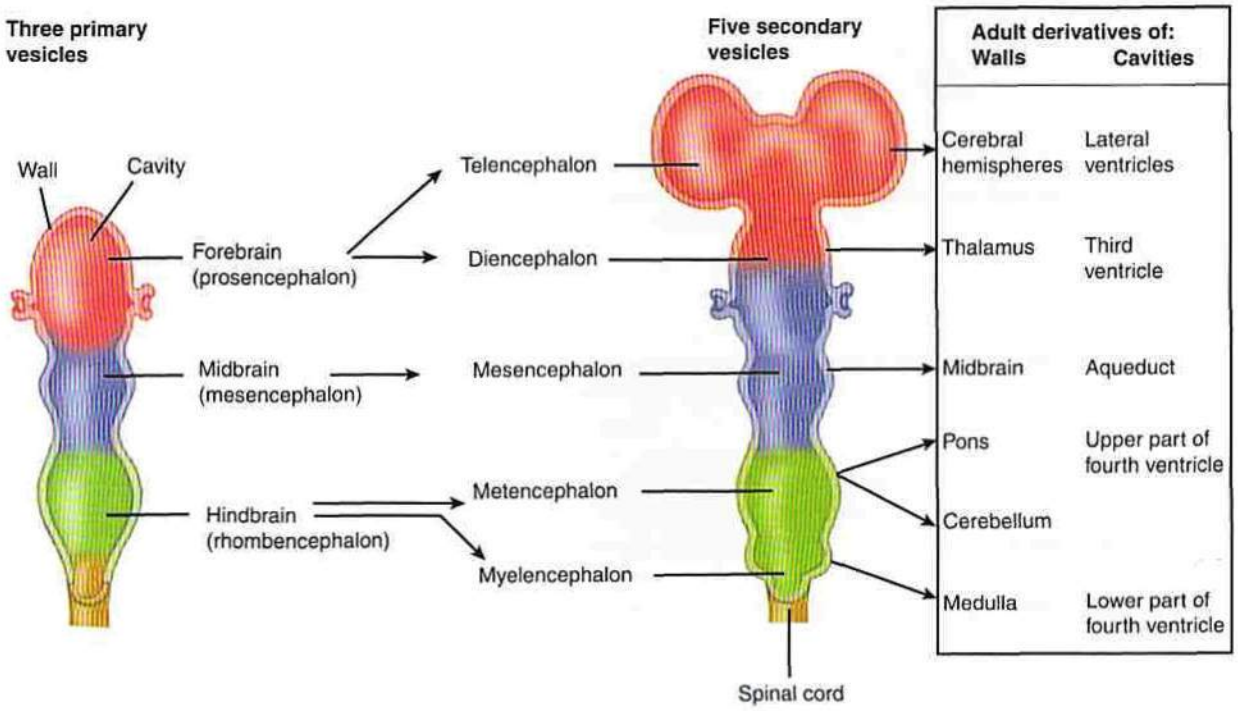


FIGURE 6-5. Development of brain vesicles.

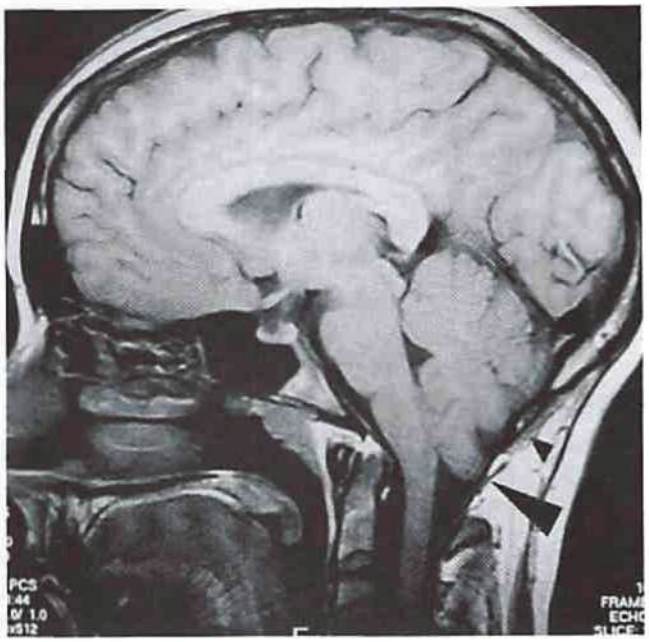


FIGURE 6-6. Arnold-Chiari syndrome type I. The black arrows point to cerebellar tonsils herniating through the foramen magnum. (Reproduced, with permission, from Brunicardi F. *Schwartz's Manual of Surgery*. New York: McGraw-Hill, 2006: 1651.)

PRESENTATION

- Type I is asymptomatic.
- Type II may present with:
  - Difficulty swallowing (due to compression of the nucleus ambiguus).
  - Loss of pain/temperature sensation along the back of the neck and shoulders secondary to syringomyelia, which interrupts the ascending afferent sensory fibers in the anterolateral tract.

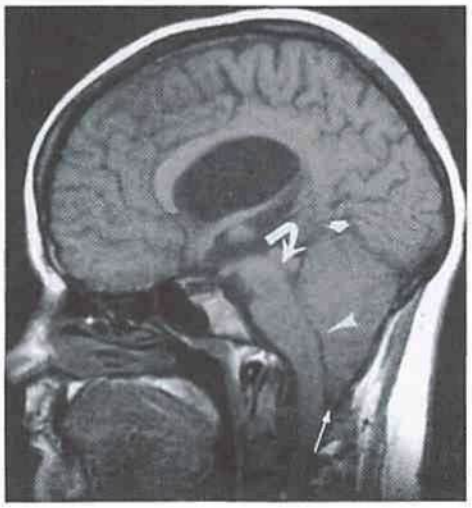


FIGURE 6-7. Arnold-Chiari syndrome type II. A small posterior fossa is present, resulting in cerebellar tonsillar ectopia (long arrow), towering of the cerebellum (short arrow), breaking of the tectum (curved arrow), and compression of the fourth ventricle (arrowhead) with resulting hydrocephalus. Partial agenesis of the rostrum and splenium of the corpus callosum is noted. (Reproduced, with permission, from Chen M. *Basic Radiology*. McGraw-Hill, 2006: 334.)

- Mental retardation secondary to coincident meningocele, a visible cyst containing spinal cord matter protruding from the dorsum of the spine.
- Hydrocephalus due to occlusion of CSF flow through the foramen magnum.

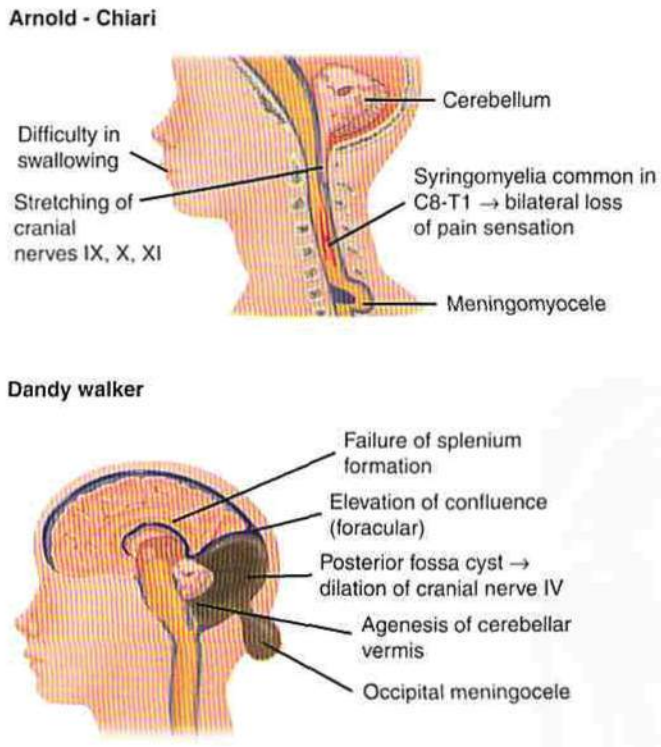
Prognosis

Depends on the degree of severity.

- Type I: Normal life span.
- Type II: 15% die within 1 year of birth. Death is usually due to cranial nerve and brain stem dysfunction resulting in respiratory failure.

Dandy-Walker Syndrome

Dandy-Walker syndrome occurs in 1 in 25,000 births, far less common than Arnold-Chiari syndrome. The associated cerebellar hypoplasia is often caused by viruses, posterior fossa trauma, or vitamin B_2 deficiency. This results in failure of the foramina of Luschka and Magendie to open, leading to dilation of the fourth ventricle, causing occipital meningocele and eventually agenesis of the cerebellar vermis and splenium of the corpus callosum (see Figure 6-8).



Arnold-Chiari syndrome

Features:

- Breaking of tectal plate
- Aqueductal stenosis
- Kinking and transforaminal herniation
- Herniation and unrolling of vermis into vertebral canal

Type 1:

- Asymptomatic
- More common (1:1000)
- Meningomyocele is common
- Only tonsils herniate

Type 2:

- Small posterior fossa
- True herniation of brainstem

Dandy-Walker syndrome

Causes:

- Virus
- Lack of vitamin B_2
- Posterior fossa trauma

Incidence at birth, 1:25000

FIGURE 6-8. Comparison of Arnold-Chiari syndrome types I and II and Dandy-Walker syndrome. Arnold-Chiari is much more common, and involves a "falling through" of the cerebellum. Dandy-Walker is an agenesis of the cerebellum and a "blowing up" of the posterior fossa.

Presentation

Severe mental retardation and ataxia.

Prognosis

Varies dramatically. Some patients may lead completely normal lives, while others die soon after birth. Overall, it carries a 12%–50% mortality rate.

MNEMONIC

Dandy-**Walker** has trouble with **walking.**

Hydrocephalus

Hydrocephalus is defined as increased intracranial pressure (ICP). The most common congenital cause is aqueductal stenosis, a consequence of maternal infection (e.g., CMV or toxoplasmosis).

Presentation

Enlarged cranium with thinning of the bones of the skull and cerebral cortex. Cranial sutures (fissures between plates of bones that make up the skull) do not close until many years after birth. The increased intracranial pressure pushes the bones apart, enlarging the skull and head circumference.

Treatment

Placement of an extraventricular shunt (e.g., from the ventricle to the peritoneum).

Prognosis

Depends on the degree of increased pressure. In severe cases, brain tissue is compressed and cannot form properly, resulting in mental retardation.

Microcephaly

Microcephaly is characterized by small brain size. Growth of the skull depends on growth of the brain, so the head circumference is decreased secondary to the underlying defect in brain development. This may be due to genetic causes, prenatal infection, or exposure to teratogens (e.g., toxoplasmosis, alcohol, radiation).

Presentation

Small head size; 50% of patients have some degree of mental retardation.

Prognosis

Depends on the severity and degree of mental retardation.

Holoprosencephaly

Failure of midline cleavage of the forebrain. This can be seen in severe fetal alcohol syndrome and Patau's syndrome (trisomy 13). The forebrain may lack midline features, including the corpus callosum, resulting in a single ventricle in the middle of the brain rather than bilateral ventricles (see Figure 6-9).

Presentation

Clinical symptoms can range from mild to severe. Extremely mild cases may be only identified via a sincle incisor. Severe cases, however, can present with cyclopleqia, a lack of central midline structures, and a single ventricle. The degree of mental retardation depends on the extent to which structures are affected.

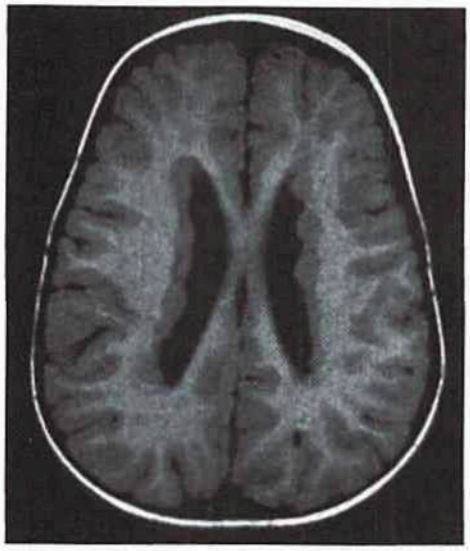


FIGURE 6-9. Holoprosencephaly. Note the lack of brain matter dividing the two hemispheres. (Reproduced, with permission, from Chen F. *Basic Radiology*. New York: McGraw-Hill, 2006: 332.)

KEY FACT

Fetal alcohol syndrome is the most common cause of mental retardation. It is characterized by microcephaly, congenital heart disease, and in severe cases, holoprosencephaly.

Prognosis

Depends on severity. In mild cases, individuals may lead a normal life; in more severe cases, the condition may result in mental retardation and early death.

KEY FACT

Patau's syndrome (trisomy 13) is characterized by holoprosencephaly, microcephaly, polydactyly, cleft palate, narrow fingernails, and apneic spells. It is the most rare form of the viable trisomies (21, 18, and 13). Death occurs within 1 year.

Key Terms

- Gyrus (pl. *gyri*) = outpouching fold of the brain.
- Sulcus = groove between the gyri.
- Cortex = layers of gray matter that overlie the deeper white matter of the brain.
- Sylvian fissure = oblique groove that divides the temporal lobe from the parietal and frontal lobes.
- Central sulcus = major sulcus that runs coronally, dividing the frontal lobe from the parietal lobe.
- Nuclei = collection of neuron cell bodies (as opposed to axons), usually sharing a common function.

MNEMONIC

The meninges **PAD** the brain from inside out.
Pia mater
Arachnoid
Dura mater

Meninges

Connective tissue that surrounds the CNS, including the brain and spinal cord. The meninges consist of **three** membranes:

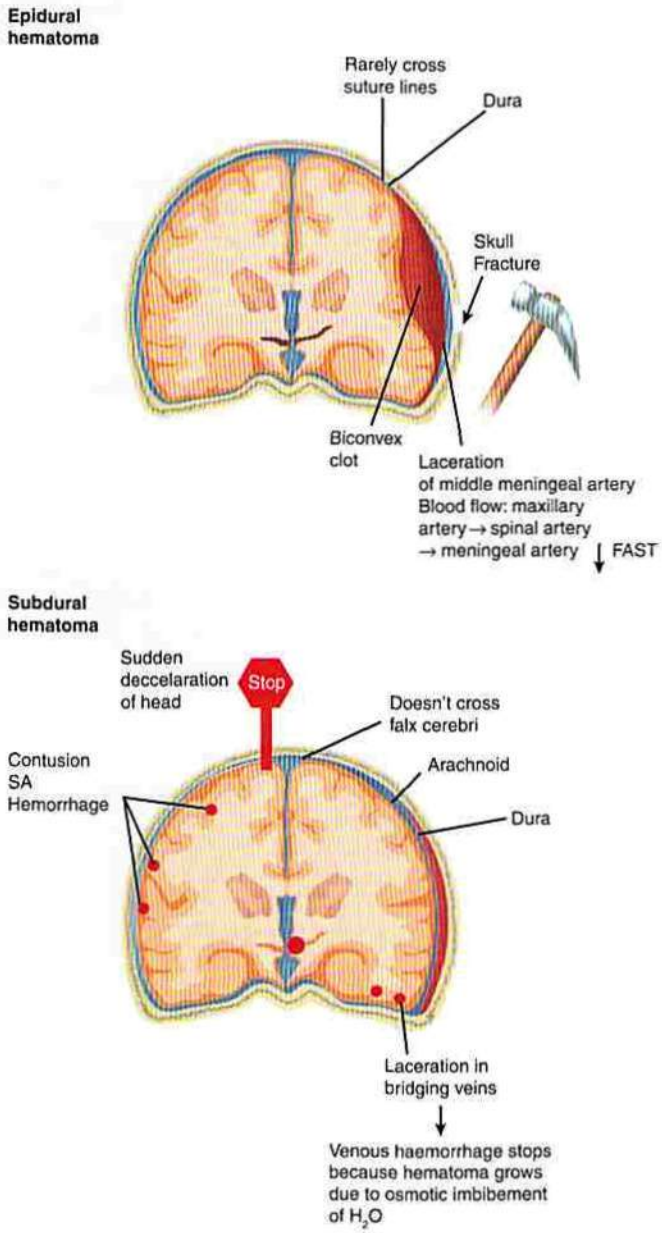
- **Pia mater:** Delicate and highly **vascular;** closely covers the surface of the brain and spinal cord.
- **Arachnoid:** Delicate, **nonvascular** layer with **granulations** that absorb CSF.
- **Dura mater:** Dense, tough exterior layer.

The membranes form several potential and real spaces:

- **Subarachnoid space:** Lies between the pia and the arachnoid and contains CSF. This space terminates at the S2 vertebra, where the CSF is produced and resorbed and where blood from intracerebral hemorrhages accumulates.
- **Subdural space:** Lies between the arachnoid and the dura and is traversed by "**bridging veins**" in the brain.
- **Epidural space:** Potential space outside the dura that contains meningeal arteries. In the spinal cord, it contains fatty areolar tissue, lymphatics, and venous plexuses.

Pathology of the Meninges

Meningeal tissues can be involved in several pathologic processes, including bleeding, infection, and cancer. Bleeding in the meningeal spaces presents differently depending on the source and location of the bleed (see Figure 6-10).



Epidural hematoma

- Lucid interval in 50% ("talk and die" syndrome)

Subdural hematoma

- More common than epidural
- Always cause brain damage
- Elderly, diabetic, atrophy
- May be associated with contusion, subarachnoid, and hemorrhage

Subarachnoid hemorrhage

- Ruptured berry aneurysm
- "Worst headache of my life"
- Marfan, Ehlers-Danlos type 4
- Apolycystic disease, HTN, smoking, blacks, ↑ age

Intracerebral/parenchymal hemorrhage

- HTN, trauma, infarct
- Amyloid angiopathy, DM
- Charcot Bouchard aneurysm from HTN
- Basal ganglia thalamus

FIGURE 6-10. Comparison of epidural and subdural hemorrhages.

Subarachnoid Hemorrhage (SAH)

Usually due to a ruptured aneurysm. Presents as the sudden onset of the "worst headache of life." Imaging may show enhancement in the area of the hemorrhage. Risk factors include hypertension, smoking, and older age.

Subdural Hemorrhage

Usually due to deceleration injury resulting in disruption of the bridging veins. The bleeding is venous and therefore accumulates slowly. They are often accompanied by intracranial bleeds or contusions and present as decline in mental status over days to weeks. Imaging shows enhancement of a crescent-shaped area that does *not* cross the midline or any dural attachments (suture lines). Subdural hemorrhage is seen most often in the elderly, alcoholics, and shaken babies.

Epidural Hemorrhage

Usually due to blunt head trauma resulting in disruption of the meningeal arteries. Imaging shows a biconcave, lens-shaped enhancement with smooth borders. A lucid interval during which the patient is completely asymptomatic may preceed a sudden decline in mental status and "drop and die" syndrome.

KEY FACT

Meningismal signs
- Kernig's sign: Inability to straighten knee when hip is flesed at 90 degrees
- Brudxinski's sign: Laying flat on their back, with passive flexion of neck, patent flexes knees.

Meningitis

Inflammation of the meninges is often caused by a bacterial or viral infection.

- Bacterial meningitis: High fever, headache, nuchal rigidity, Kernig's and Brudzinski's signs. The organism involved depends on the age of the patient.
- Viral meningitis (aseptic meningitis): Similar to bacterial, but less acute in onset with less severe symptoms.
- Fungal meningitis: Seen in immunocompromised patients, often due to *Cryptococcus*.
- Diagnosis made by lumbar puncture (see Figure 6-11 and Table 6-4).

Meningioma

Benign, well-circumscribed, slow-growing tumors. These are more common in females than males. The patient often presents with headache and can be treated by resection or rarely radiation. These tumors are slow-growing and carry a good prognosis.

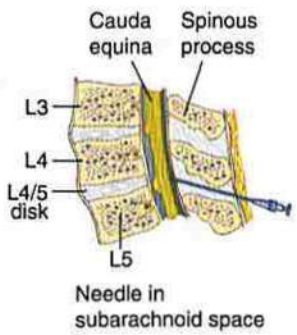


FIGURE 6-11. Lumbar puncture placement. The correct position may be located by finding the space between the spinous processes at the level of the iliac spine.

TABLE 6-4. Cerebrospinal Fluid Characteristics of the Different Types of Meningitis

	BACTERIAL	FUNGAL	VIRAL
WBC	PMN predominant	Lymphocyte predominant	Lymphocyte predominant
Glucose	Decreased	Decreased	Normal
Protein	Elevated	Slightly elevated	Slightly elevated

CARCINOMATOUS MENINGITIS

The meningeal space is a common site for metastatic spread from cancer outside the CNS. This condition is life-threatening and may present with mental status changes and headaches. Cranial nerve deficits may be found on clinical exam. Treatment consists of chemotherapy applied to the CSF.

Ventricles

Ventricles are interconnected spaces in the skull that contain CSF. CSF buffers the brain from impact, transports hormones, and removes waste products. CSF is produced by the **choroid plexus**, a tissue rich in blood vessels and covered with ciliated ependymal cells. It projects into the lateral, third, and fourth ventricles, and contributes to the **blood-brain barrier (BBB)**, a tight barrier that separates circulating blood from the CSF. Other components of the BBB are the following:

- Tight junctions between capillary endothelial cells.
- Basement membrane.
- Astrocyte processes.

The permeability of the BBB is characterized by:

- Increased permeability to nonpolar/lipid-soluble substances vs. polar/water-soluble substances.
- Permeability to glucose and amino acids via a carrier-mediated transport mechanism.
- Some areas of total permeability, such as the **area postrema** and the **neurohypophysis/hypothalamus.**

VENTRICULAR SYSTEM (SEE FIGURE 6-12)

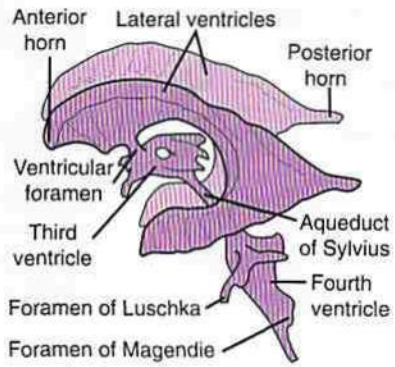
- Two lateral ventricles communicate with the third ventricle through the foramina of Monro.
- The third ventricle communicates with the fourth ventricle through the cerebral aqueduct of Sylvius.
- The **fourth ventricle** communicates with the subarachnoid space via three outlet foramina: two **foramina of Luschka** and one **foramen of Magendie.**

KEY FACT

The aqueduct is the most common site of stenosis.

Hydrocephalus is caused by dilation of the ventricles and excessive accumulation of CSF. There are several forms:

- **Noncommunicating hydrocephalus:** Obstruction between or within the ventricles (e.g., congenital aqueductal stenosis).
- **Communicating hydrocephalus:** Can arise from three causes: (1) CSF oversecretion (choroid papilloma); (2) CSF circulation blockage (tumor in the subarachnoid space); and (3) poor CSF absorption (meningitis, post-meningitis adhesions, dural venous sinus thrombosis).



Lateral ventricle → Third ventricle via foramen of Monro.
Third ventricle → Fourth ventricle via aqueduct of Sylvius.
Fourth ventricle → Subarachnoid space via:
Foramina of Luschka = Lateral.
Foramen of Magendie = Medial.

FIGURE 6-12. Ventricular system. Note the flow of CSF from the lateral ventricles through the foramen of monro to the third ventricle, through the aqueduct to the fourth ventricle, into the subarachnoid space via arachnoid granulations, and back into the dural venous sinuses.

MNEMONIC

Triad for normal-pressure hydrocephalus: **wacky, wobbly, wet.**
1. Progressive dementia (wacky)
2. Ataxic gait (wobbly)
3. Urinary incontinence (wet)

- **Normal pressure hydrocephalus:** Decreased absorption of CSF by the arachnoid mater (e.g., meningeal hemorrhage).
- **Hydrocephalus ex vacuo:** Overall loss of brain tissue, as seen in neurodegenerative diseases such as Alzheimer's disease.
- **Pseudotumor cerebri** (benign intracranial hypertension): Increased resistance to CSF outflow. Seen in young obese women who present with headache and visual changes. Exam reveals papilledema, increased ICP (detected by lumbar puncture), and slit-like ventricles on neuroimaging.

The site of ventricular dilation can point to the site of mechanical blockage in CSF flow:

1. Dilated lateral ventricles → blockage in the foramen of Monro.
2. Dilated third ventricle and lateral ventricles → blockage in the aqueduct.
3. Dilated aqueduct, third ventricle, and lateral ventricle → blockage in the fourth ventricle.

MNEMONIC

Pseudotumor cerebri can be caused by **A LOT A Stuff:**
Amiodarone
Lupus
Oral contraceptives
Tetracycline
Vitamin **A** in high doses
Steroids

Blood Supply

The Circle of Willis

The circle of Willis is a network of arteries that sits at the base of the brain in the area encircling the optic chiasm and pituitary gland. It is fed by two major arterial systems: the internal carotids (anterior circulation) and the vertebrobasilar systems (posterior circulation; see Figure 6-13).

The internal carotid artery gives rise to several branches before joining the circle of Willis:

- Ophthalmic artery: The first branch of the internal carotid gives rise to the **central artery of the retina.** Its occlusion leads to sudden-onset blindness.
- Anterior choroidal artery: Supplies the lateral geniculate body (associated with vision), globus pallidus, and internal capsule.

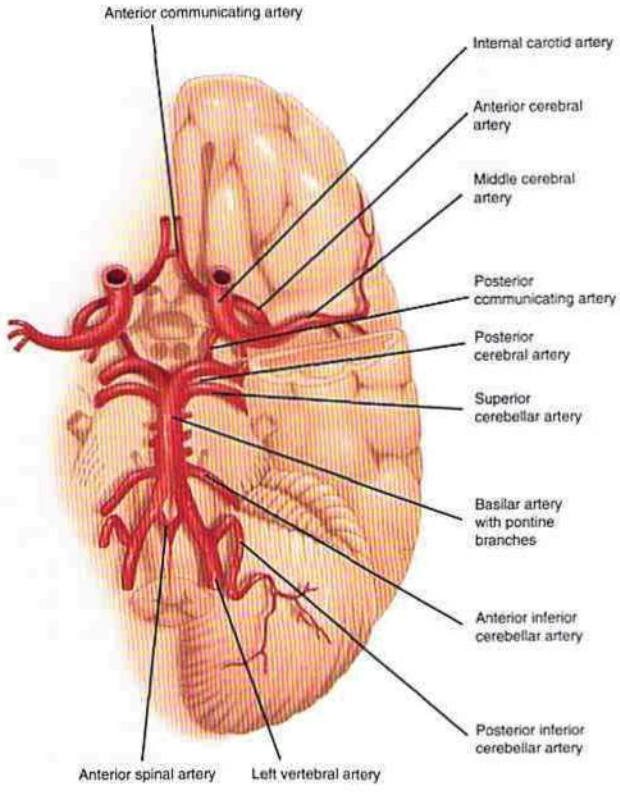


FIGURE 6-13. The circle of Willis, viewed from the inferior aspect of the brain, looking up from below. At the center are the optic chiasm and the pituitary gland. Note how the basilar artery sprawls over the pons and how CN III emerges between the posterior communicating artery (PCA) and the superior cerebellar artery. The location of CN III predisposes it to compression by PCA aneurysms.

Major components of the circle of Willis:

- Anterior cerebral artery (ACA): Supplies the medial aspect of the frontal lobes, including the lower extremity motor and sensory cortices.
- Anterior communicating artery: Most common site of **aneurysm** in the circle of Willis, giving rise to **bitemporal lower quadrantanopia.**
- Middle cerebral artery (MCA): Supplies the lateral aspect of the brain, the trunk-face-upper extremity area of motor and sensory cortices, and Broca's and Wernicke's speech areas.
  - The lateral striate branches of the MCA, which supply the internal capsule and basal ganglia, are known as the arteries of stroke (see Table 6-5).
- Posterior cerebral artery (PCA): Supplies the occipital lobe.
- Posterior communicating artery: Another common site of aneurysms, which may be associated with CN III palsy.

TABLE 6-5. Neurologic Deficits Associated With Stroke

ACA	MCA	PCA
Lower extremity weakness	Aphasias (if dominant hemisphere); apraxias (if nondominant hemisphere); face and upper extremity weakness	Visual field deficits with macular sparing

Vertebrobasilar system:

- Anterior spinal artery: Supplies the ventral portion of the spinal cord.
- Posterior inferior cerebellar artery (PICA): Supplies the medulla and the posterior cerebellum.
- Anterior inferior cerebellar artery (AICA): Supplies the pons, CN VII, and the inferior surface of the cerebellum.
- Pontine arteries: Supply the base of the pons, including the corticospinal fibers and CN VI.
- Superior cerebellar artery (SCA): Supplies the pons, the superior surface of the cerebellum, and CN VII and VIII.

Dural Veins and Sinuses

KEY FACT

The dural venous sinuses provide pathogens and neoplastic cells with a valveless path from the face/sinuses through bridging veins to the brain.

Superior cerebral ("bridging") veins drain into the superior sagittal sinus and the right transverse sinus to the confluence of sinuses. Meanwhile, the **great cerebral vein of Galen** drains deep cerebral veins into the **straight sinus,** though the left transverse sinus and to the confluence of sinuses (see Figure 6-14). The superior sagittal sinus, great cerebral vein, cavernous sinuses (via the petrosal sinuses), and occipital sinus all drain into the confluence of sinuses, which in turn empties into the transverse, sigmoid, and finally the internal jugular vein, which drains into the superior vena cava.

CLINICAL CORRELATION

Cavernous sinus syndrome results from increased pressure in the cavernous sinus → **ophthalmoplegia and facial sensory loss.**

The **cavernous sinus** is a collection of venous sinuses surrounding the pituitary gland. It drains blood from the eye and superficial cortex and feeds into the jugular vein (see Figure 6-15).

The cavernous sinus contains several structures.

- CN III, CN IV, V1, V2, VI, and postganglionic sympathetic fibers that supply the orbit.
- CN III, CN IV, V1, and V2 are attached to the wall of the sinus; CN VI is free-floating.

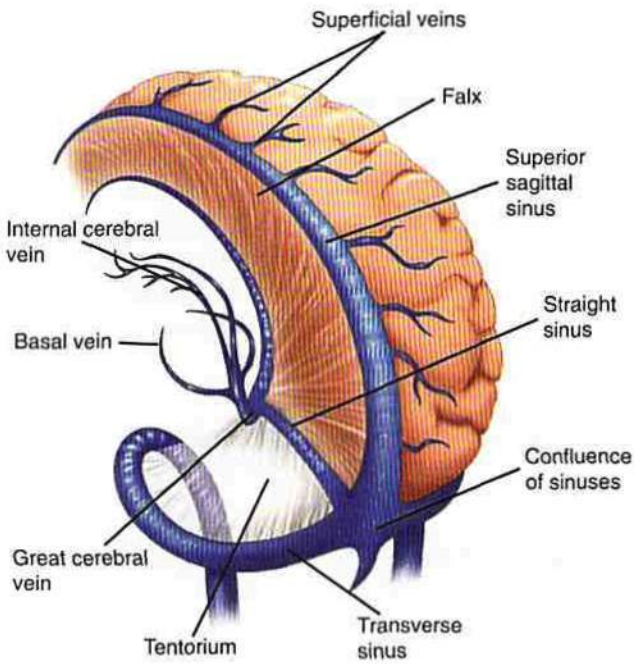


FIGURE 6-14. Venous sinuses of the brain.

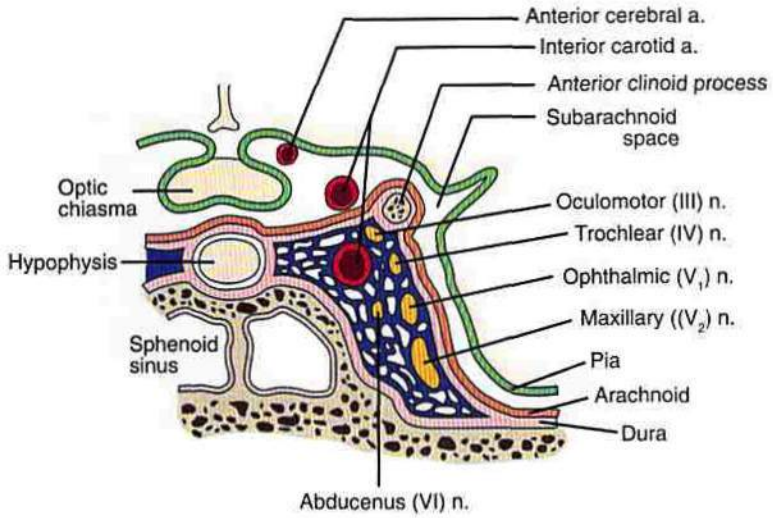


FIGURE 6-15. Cavernous sinus. Coronal cut through the cavernous sinus showing passage of cranial nerves and internal carotid through the sinus. (Adapted, with permission, from Kasper DL, Braunwald E, Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 2438.)

- The internal carotid arteries pass through both sides of the sinus.
- Venous drainage from the face drains to the cavernous sinus, providing a route by which skin infections can reach the brain.

Cerebral Cortex

The cortex is composed of specialized regions which are responsible for specific functions. Thus, injury and lesions in different areas of the brain produce deficits appropriate to the function of that area (see Figure 6-16). Brodmann labeled different areas of the brain by number; some of these areas are still referred to by these numbers (see Figure 6-17).

Organization

The cerebral cortex is composed of six layers of cells; the relative size of each layer varies among regions of the brain. Each layer consists of different types of cells and is specialized to send and receive input to and from different areas of the brain. Layer 5 in the primary motor cortex is known for the large motor neurons of the corticospinal tracts known as **Betz cells.**

The cortex is divided into the frontal, parietal, temporal, and occipital lobes (see Figure 6-16). Major fissures and sulci (grooves) separate the different lobes: The **sylvian fissure** divides the temporal lobes from the rest of the cortex; the **central sulcus** divides the frontal from the parietal lobe; and the **sagittal sulcus** divides the brain into the left and right hemispheres.

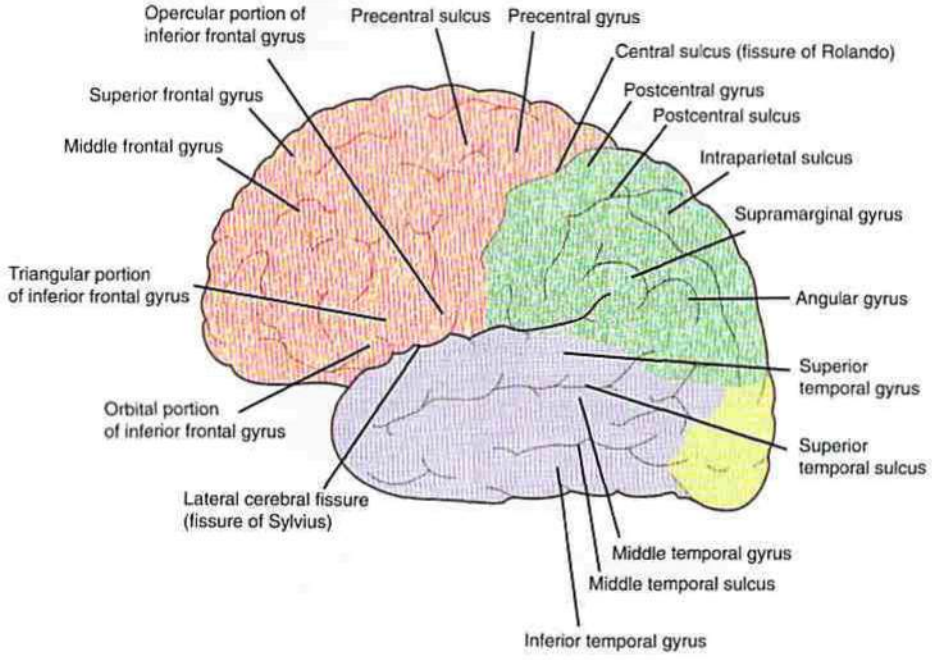
Frontal Lobe

Location

Anterior to the central sulcus.

Major Areas

Prefrontal cortex, premotor cortex, primary motor cortex, frontal eye fields, Broca's area.



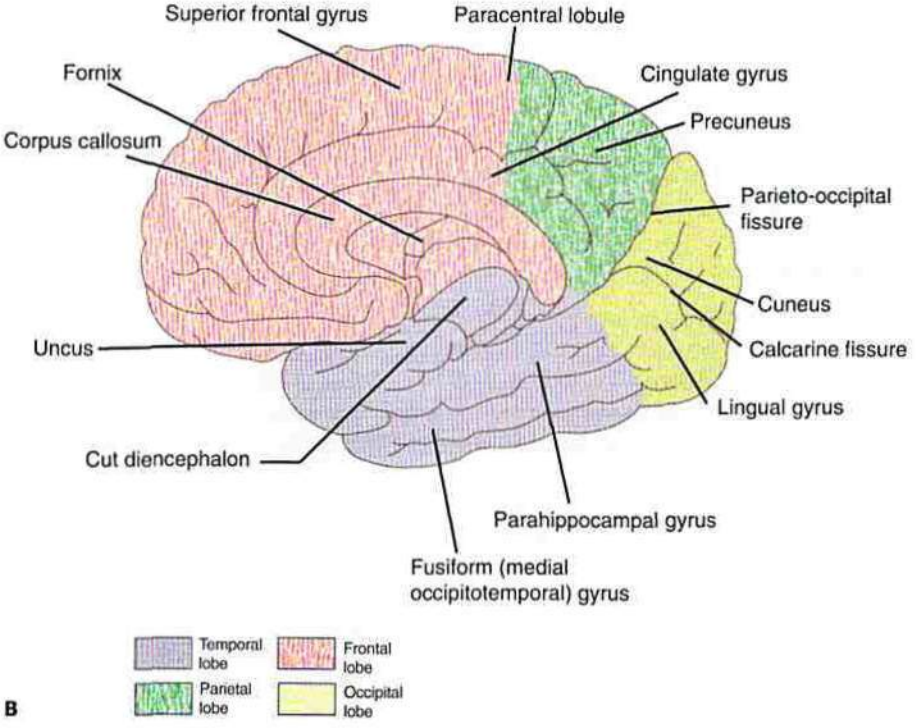


FIGURE 6-16. Basic surface anatomy of the cerebrum. (A and B) Major structures of note are the four major lobes, precentral sulcus/gyrus, central sulcus, sylvian fissure, cingulate gyrus, corpus callosum, uncus, and hippocampal gyrus.

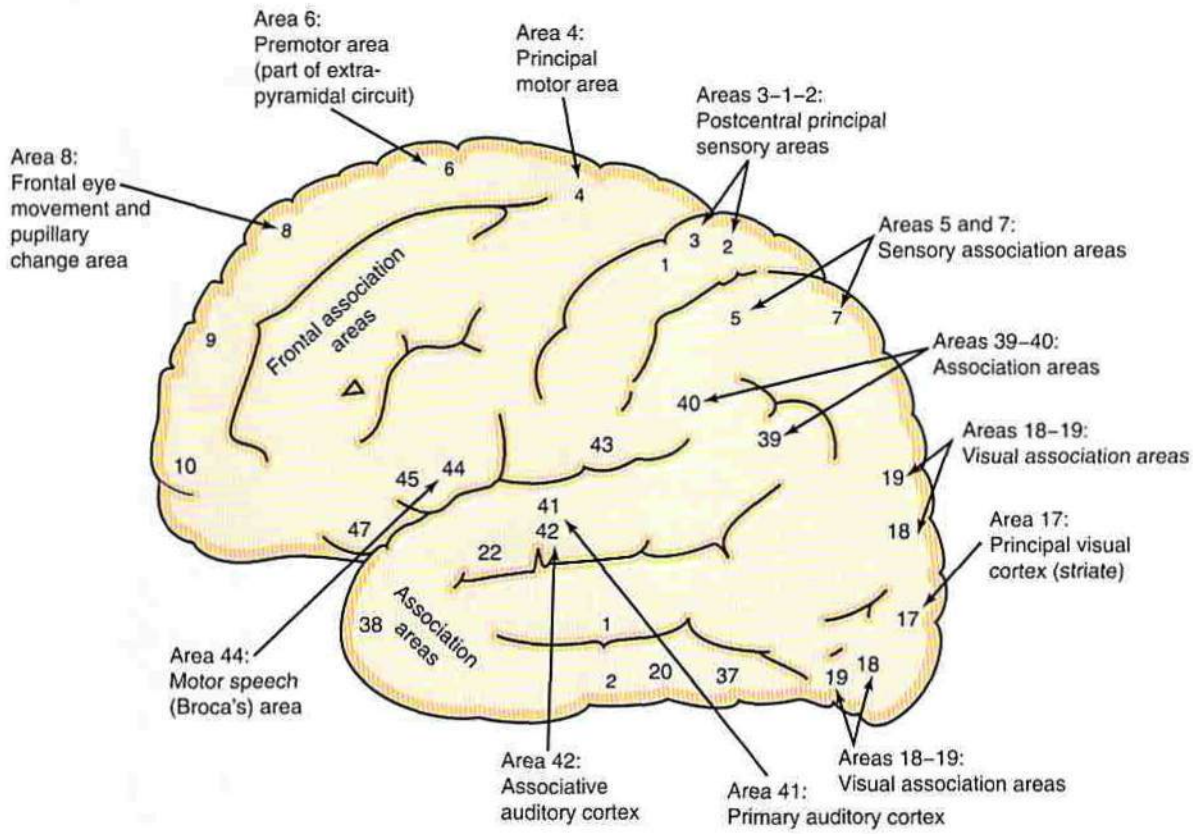


FIGURE 6-17. Brodmann's areas of the brain. Areas of note include areas 3–1–2 = primary sensory cortex; area 4 = primary motor cortex; area 8 = frontal eye fields; area 44 = Broca's area; area 22 = Wernicke's area; and area 17 = primary visual cortex. (Reproduced, with permission, from Waxman SG. *Neuroanatomy with Clinical Correlations*, 25th ed, New York: McGraw-Hill, 2003.)

FUNCTIONS

- **Movement (primary motor and premotor cortex):** Areas in charge of movement include the primary motor cortex and premotor cortex, located anterior to the central gyrus. The primary motor cortex is closest to the central sulcus, and the premotor cortex is located more anteriorly. The **premotor cortex** is responsible for **planning** movements, whereas the **primary motor cortex executes** the movements via the descending motor neurons of the corticospinal tract. Areas of the motor cortex correspond geographically to the body parts they control, as mapped out by the homunculus (see Figure 6-18).
  - Lesion of a motor strip → spastic paralysis of the contralateral body part corresponding to the damaged area.
- **Eye movements (frontal eye fields):** The frontal eye fields (also known as area 8) control eye movements.
  - Lesions of the frontal eye fields:
    - Ischemic lesion (i.e., stroke): Eyes drift toward the side that is injured,
    - Hyperactivity (i.e., seizure): Eyes drift away from the side of hyperactivity.
- **Social judgment (prefrontal cortex):** The frontal lobe is responsible for inhibiting impulsive thoughts to tailor behavior to fit social norms.
  - Lesion of the prefrontal cortex → disinhibition. For example, Phineas Gage, a formerly mild-mannered man who survived severe frontal-lobe damage, became rude, obnoxious, and defiant of social norms.

KEY FACT

Area "8" looks like eyeglasses when turned sideways!

MNEMONIC

The eyes look toward a stroke, away from a seizure.

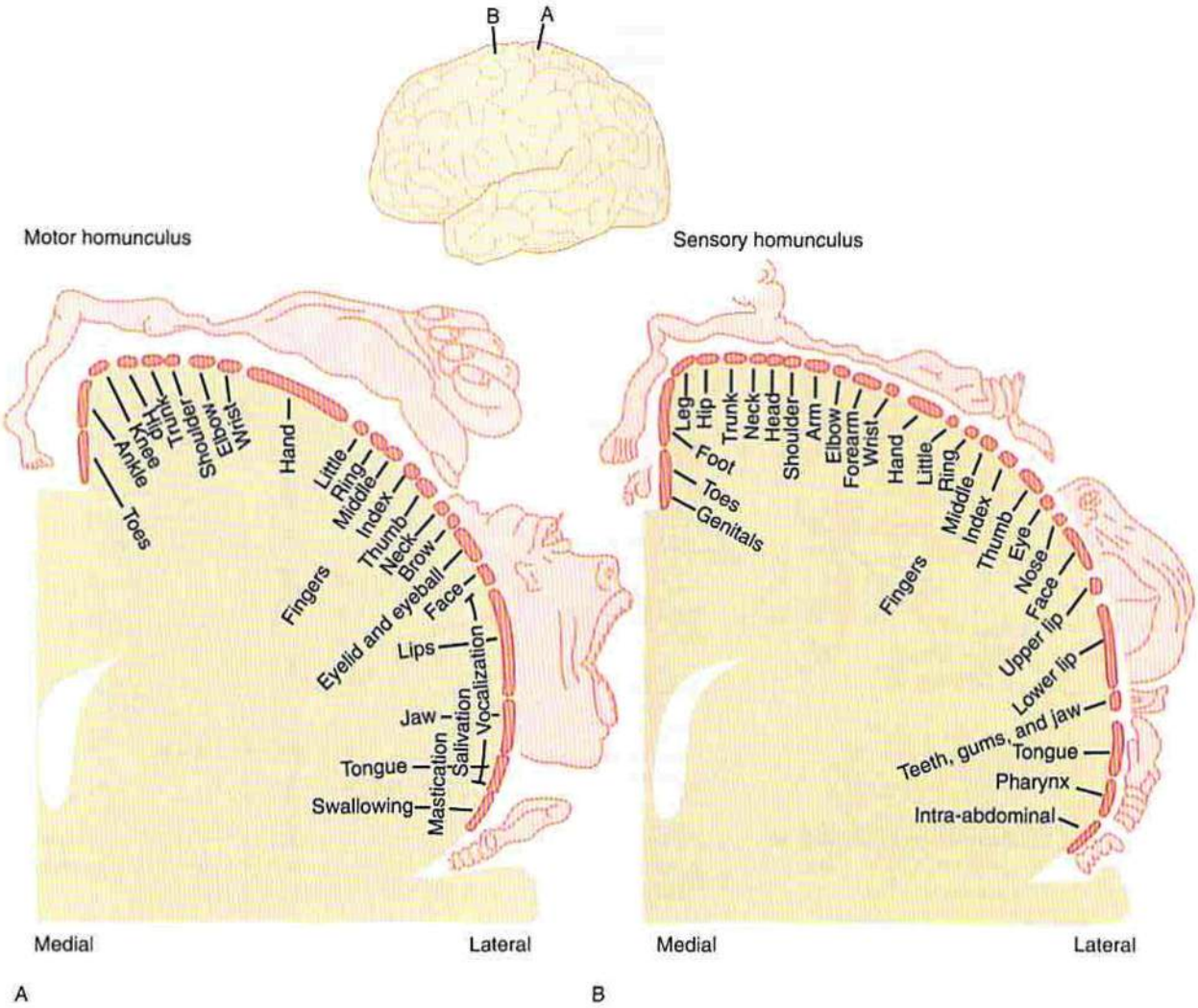


FIGURE 6-18. Motor (A) and sensory (B) homunculi. (Figure A modified, with permission, from Ropper AH, Brown RH. *Adams and Victor's Neurology*, 8th ed, New York: McGraw-Hill, 2005. Figure B modified, with permission, from Kandel ER, Schwartz JH, Jessel TM. *Principles of Neural Science*, 4th ed, New York: McGraw-Hill, 2000.)

- **Language production (Broca's area):** Broca's area or area 44 (see Figure 6-17) is involved in language production.
  - Lesion in Broca's area → inability to produce coherent speech. Words spoken by the patient are incomprehensible. Patients appear to have difficulty forming words and speak very slowly and laboriously. Comprehension is intact.
- **Executive functions:** Concentration, orientation, abstraction, judgment, mood, and inhibition of primitive reflexes.
  - Lesion can lead to unmasking of primitive reflexes such as suckling, grasp, and rooting reflexes.

Blood Supply

Anterior cerebral artery (ACA) and middle cerebral artery (MCA).

Parietal Lobe

The parietal lobes are located on the lateral to the sagittal sulcus and posterior to the frontal lobes.

Location

Posterior to the central sulcus.

Major Areas

Primary sensory cortex.

Functions

- **Sensation (primary sensory cortex):** The primary sensory cortex is just posterior to the central sulcus and the primary motor cortex. Like the motor cortex, a sensory homunculus represents the anatomical correlations (see Figure 6-17). The ascending spinal thalamic and dorsal spinal tracts synapse in the thalamus and project to the primary sensory cortex. The primary sensory cortex then sends projections to the secondary and association cortices that integrate sensory components into a cohesive interpretation.
  - Lesion → loss of tactile sensation in body parts corresponding to the injured area of the brain.
- **Spatial relationships:** Determination of right and left.
  - Lesion → **Gerstmann's syndrome** (lesion of the inferior parietal lobe of the dominant hemisphere).
    - Right and left confusion.
    - Finger agnosia: Inability to name and recognize one's own fingers or others' fingers.
    - Dysgraphia and alexia: Inability to write and read.
    - Dyscalculia: Inability to make arithmetic calculations.
- **Vision:** Contralateral hemianopia and lower quadrantic hemianopia are due to injury to the optic tract that passes through the parietal lobe on the way to the occipital lobe.
- **Attention:** Visual and cognitive attention.
  - Unilateral lesion: **Contralateral neglect,** for example, an individual with a right parietal lesion may fail to put clothes on their left side (e.g., will only put on the right shoe). May also reproduce the classic drawing of a clock with all the numbers on one side.
  - Lesion of the dominant hemisphere: **Apraxia,** or inability to carry out learned movements. Patients often are unable to perform an action when commanded to, but are able to imitate or perform the action in response to other triggering stimuli.
  - Bilateral lesions: **Balint's syndrome,** a form of visual agnosia, in which patients are unable to scan visual space and to grasp an object in space.

KEY FACT

Clarification: **Dys**lexia is congenital; **a**lexia is **a**cquired.

Blood Supply

MCA and ACA supply the region of the homunculus which supplies the leg.

KEY FACT

The MCA, due to its central location at the branch point of the carotid artery in the circle of Willis (see Figure 6-13), is the artery most commonly involved in an embolic stroke.

Occipital Lobe

Location

Most posterior region of the brain.

Major Areas

Primary visual cortex, association visual cortex.

Functions

- **Vision (primary and association visual cortices):**
  - Visual pathway: Retina → fibers cross at the optic chiasm → synapse at the lateral geniculate nucleus (LGN) → primary visual cortex within the occipital lobe (see Figure 6-17).
  - Visual signals are processed through inputs from the primary visual cortex to the visual association cortex in the occipital lobe.
- **Visual recognition (association cortices):**
  - Lesion → visual agnosia, the inability to recognize objects one sees.
  - Lesion → alexia without agraphia, the acquired inability to read while retaining the ability to write.

Blood Supply

Posterior cerebral artery (PCA). The calcarine cortex is supplied by the PCA, but the macula is supplied by the MCA.

Temporal Lobes

The temporal lobes form two outpouchings of the cortex and contain structures vital for hearing, memory, and emotion.

Location

Lateral to the sylvian fissure.

Major Areas

Primary auditory cortex, hippocampus, amygdala, Wernicke's area.

Functions

- **Hearing (primary auditory cortex):** Located within the sylvian fissure.
- **Auditory pathway:** Cochlea → CN VIII → medullary cochlear nuclei → fibers cross just prior to the superior olivary nuclei, along the lateral lemniscus tract → medial geniculate nucleus (MGN) → primary auditory cortex (see Figure 6-17).
  - Lesion before the CN VIII decussation, proximal to the superior olivary nuclei → unilateral hearing loss, even deafness.
  - Lesion distal to the CN VIII decussation, distal to the medullary cochlear nuclei → bilateral diminished hearing without deafness.
- **Memory (hippocampus):** The hippocampus is responsible for learning and consolidation of short-term memory, before memories are later integrated into the cortex. The hippocampus is part of the Papez circuit, which contains structures presumed to play a role in memory and emotion (see Figure 6-19).
  - Hippocampal lesion → anterograde memory loss (inability to form new memories).
- **Emotion:** The temporal lobe is part of the limbic system. Memory and emotion are intimately related, both structurally and functionally.
  - Fear: Emotional responses, such as the fear response, are mediated by the amygdala.
  - Lesion → ablation of the fear response, or **Klüver-Bucy syndrome.**
  - Klüver-Bucy syndrome includes psychic blindness (treating objects inappropriately), hypermetamorphosis (failure to recognize familiar

KEY FACT

Types of memory loss include anterograde and retrograde.
Anterograde = inability to create new memories after the injury.
Retrograde = inability to recall memories prior to the injury.

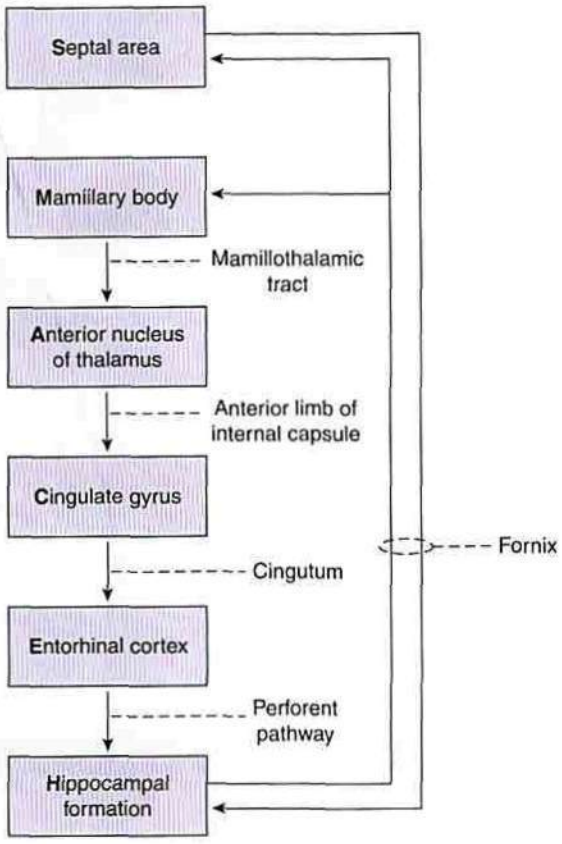


FIGURE 6-19. Papez circuit. The Papez circuit was originally proposed as a circuit for memory and emotional processing, although it is not a true circuit, structures of the "circuit" contribute to memory and emotional processing and comprise the limbic system.

objects), increased oral exploratory behavior (puts everything in one's mouth), and hypersexuality and loss of sexual preference (mounts anything in sight).

- Seizure activity → vivid hallucinations.
- **Language comprehension (Wernicke's area/area 22):** Responsible for comprehension of language as well as production of coherent language.
  - Lesion in Wernicke's area: Patients are frustrated and unable to understand what is spoken to them. They produce speech fluently that consists of real words and phrases, but does not make any sense.
  - The aphasia square (see Figure 6-20) demonstrates the various forms of aphasia.
    - Broca's aphasia: Inability to produce words.
    - Wernicke's aphasia: Inability to comprehend language and produce coherent speech.
    - Conduction aphasia: Inability to repeat after hearing a sentence.
    - Transcortical aphasia: Inability to produce words or coherent speech; however, repetition is spared,
    - Global aphasia: All language function is impaired,

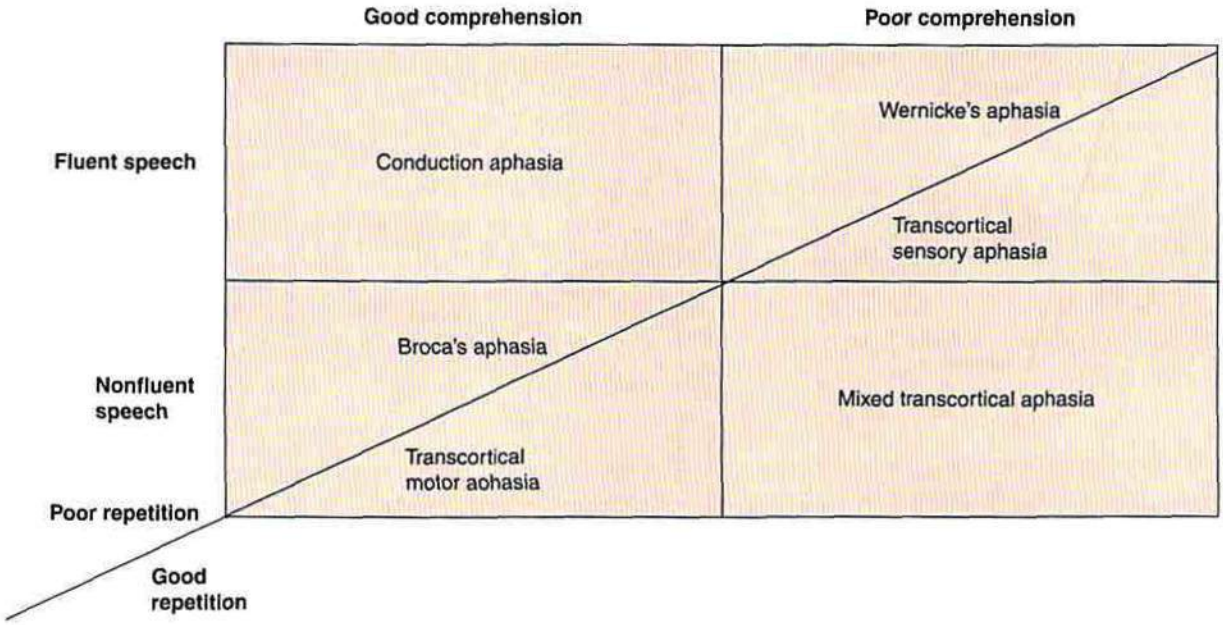


FIGURE 6-20. Aphasia square. The six most commonly tested aphasias.

DEEP BRAIN STRUCTURES

Basal Ganglia

LOCATION

Lateral to the internal capsule bilaterally.

STRUCTURES

Striatum (caudate + putamen), globus pallidus internus and externus, and the substantia nigra (see Figure 6-21).

FUNCTIONS

- **Initiation of purposeful movement** (see Figure 6-22) **via the direct and indirect pathways.**
  - Direct pathway:
    - Cortex → caudate/putamen → globus pallidus internus → thalamus → spinal cord.
    - Dopamine (DA) activates this pathway.
  - Indirect pathway:
    - Cortex → caudate/putamen → **globus pallidus externus/subthalamic nucleus** → globus pallidus internus → thalamus → spinal cord.
    - DA inhibits this pathway.
  - DA is released into the caudate/putamen from neurons that originate in the substantia nigra.
- **Lesions and corresponding deficits:**
  - Substantia nigra DA neurons → Parkinson's disease.
  - Cholinergic neurons of the caudate and putamen → Huntington's disease.
  - Subthalamic nucleus → hemiballismus.

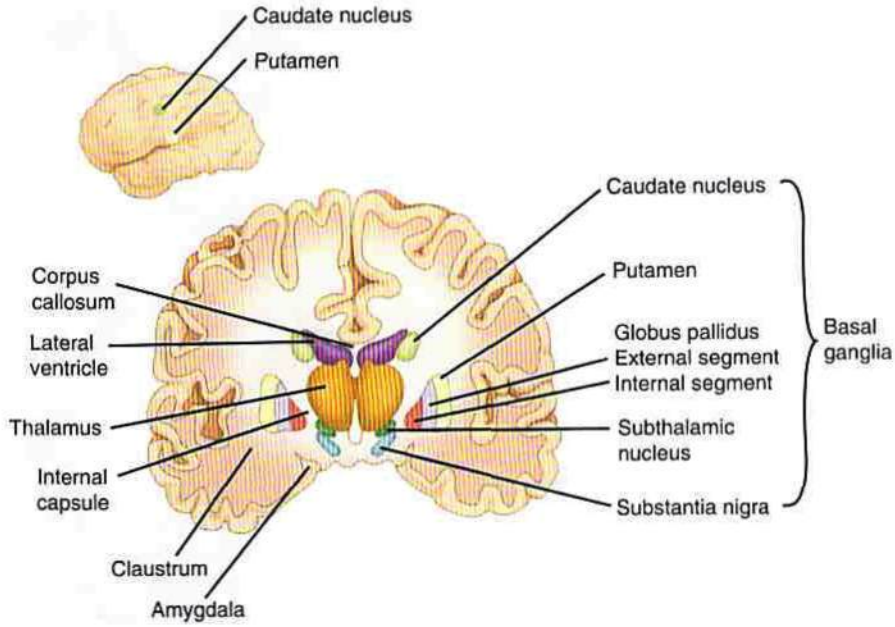


FIGURE 6-21. Major structures of the basal ganglia.

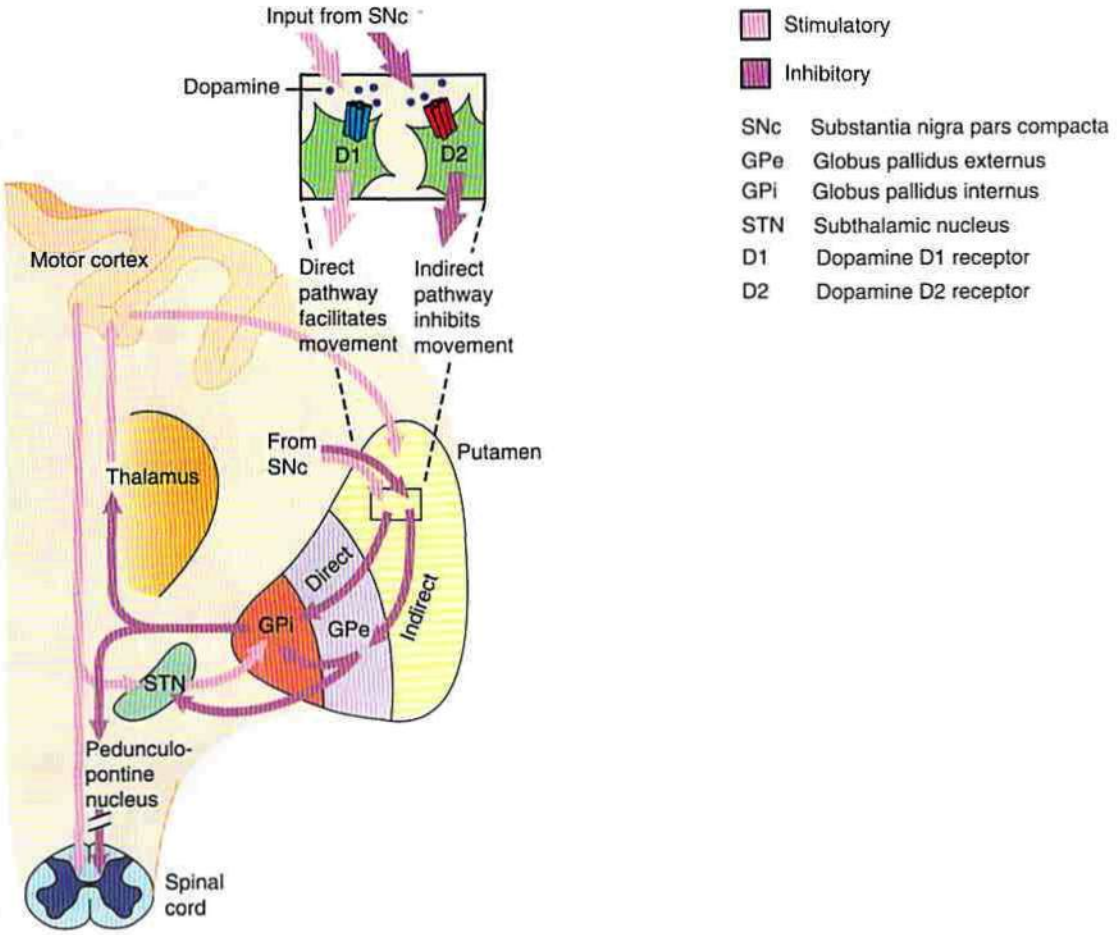


FIGURE 6-22. Basal ganglia direct and indirect pathways. (Modified, with permission, from Kandel ER, Schwartz JH, Jessel TM. *Principles of Neural Science*, 4th ed, New York: McGraw-Hill, 2000.)

Thalamus

Location

Surrounding the third ventricle, just above the midbrain.

Structures

Nine nuclei (see Table 6-6 and Figure 6-23).

Functions

- **Sensory relay station:**
  - The thalamus receives sensory input of all sensory modalities.
  - Sensory input is "filtered."
  - The thalamus sends processed signals to other areas of the cortex.
- **Emotion:** The thalamus is part of the Papez circuit, which is involved in emotion.
- **Motor relay station:** The thalamus receives input from the motor cortex and basal ganglia and sends signals to the descending motor tracts.
  - Lesion → motor and sensory deficits involving multiple areas of the body, and **thalamic pain syndrome**, which is pain perceived without an appropriate stimulus.

Blood Supply

Posterior communicating artery, anterior choroidal artery (a branch of the internal carotid artery; see Figure 6-13).

TABLE 6-6. Nuclei and Functions of the Thalamus

Nucleus	Function	Inputs	Outputs
Ventral posterior-lateral	Relay sensory information from entire body except the head.	Spinothalamic tract, tactile sensory input from trunk and extremities.	Primary sensory cortex
Ventral posterior-medial	Relay sensory information from the head.	Trigeminal tract, tactile sensory input from the face.	Primary sensory cortex
Ventrolateral	Relay motor information.	Cerebellum and basal ganglia.	Primary motor cortex
Ventroanterior	Relay motor planning information.	Motor input from frontal cortex.	Premotor cortex
Anterior nuclei	Relay emotion/memory; part of Papez circuit.	Mammillary bodies.	Cingulate gyrus
Medial dorsal	Relay cognitive information.	Amygdala, substantia nigra, and temporal cortex.	Prefrontal cortex

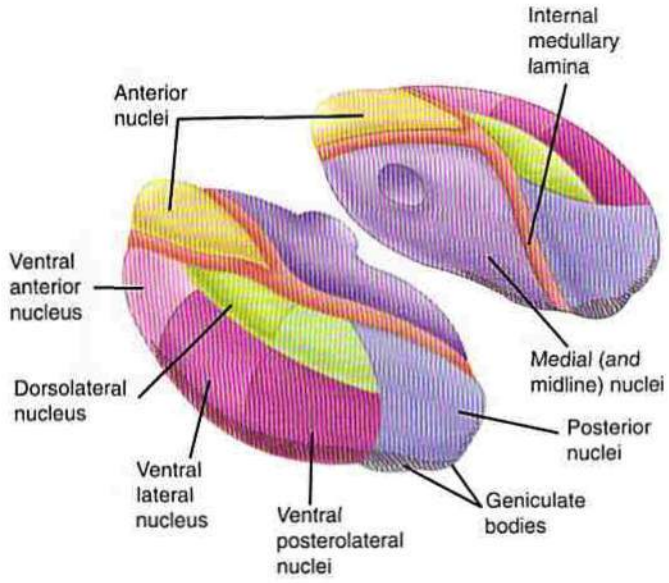


FIGURE 6-23. Thalamic nuclei. The thalamus has two lobes, one on each side of the third ventricle. The geniculate bodies include the medial and lateral geniculate bodies/nuclei that relay auditory and visual sensory information, respectively. (Modified, with permission, from Waxman SG. *Clinical Neuroanatomy*, 25th ed, New York: McGraw-Hill, 2003.)

Internal Capsule

The internal capsule is the site of convergence of all ascending and descending white matter tracts to and from the cortex.

Location

White matter lateral to the thalamus and medial to the striatum (caudate and putamen; see Figure 6-24).

Divisions

Anterior limb, posterior limb, and genu (the bend between the anterior and posterior limbs).

- Anterior limb: Ascending sensory fibers.
- Posterior limb: Descending corticospinal tract.
- Genu: The bend or "elbow"; descending corticobulbar tract.

Lesion → motor (genu, posterior limb) and sensory (anterior limb) deficits involving multiple areas of the body.

Blood Supply

Anterior limb from the medial striate branches from the ACA and lenticulostriate branches from the MCA.

Hypothalamus

The hypothalamus is involved in homeostasis and instinctive actions, such as eating, drinking, sleeping, and sex. Like the thalamus, it is divided into several nuclei controlling these functions (see Figure 6-25 and Table 6-7).

KEY FACT

Lesions of the **internal capsule** are more likely to affect multiple areas of the body compared to lesions of the motor or sensory cortex. Cortical lesions generally involve isolated parts of the body, depending on the affected segment of the homunculus.

KEY FACT

The **lateral striate arteries** are the penetrating arteries of the MCA and are called the "arteries of stroke" because they are most often affected in stroke and in **Charcot-Bouchard microaneurysms.** Charcot-Bouchard microaneurysms occur in the walls of small penetrating vessels weakened from chronic hypertension.

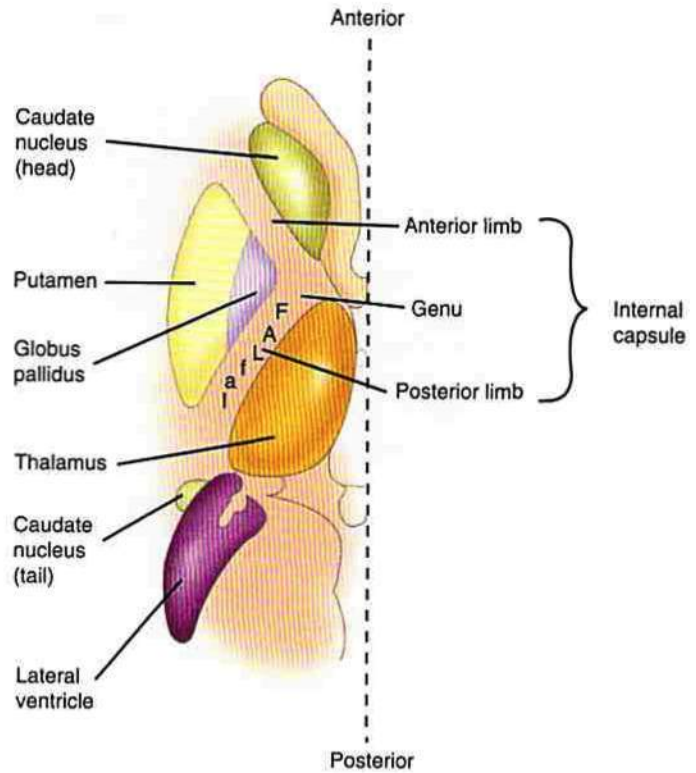


FIGURE 6-24. Axial cut of the brain through the internal capsule. Notice that descending motor fibers for the face, arm, and leg (F, A, and L) run in front of ascending sensory fibers (f, a, and l) in the posterior limb of the internal capsule.

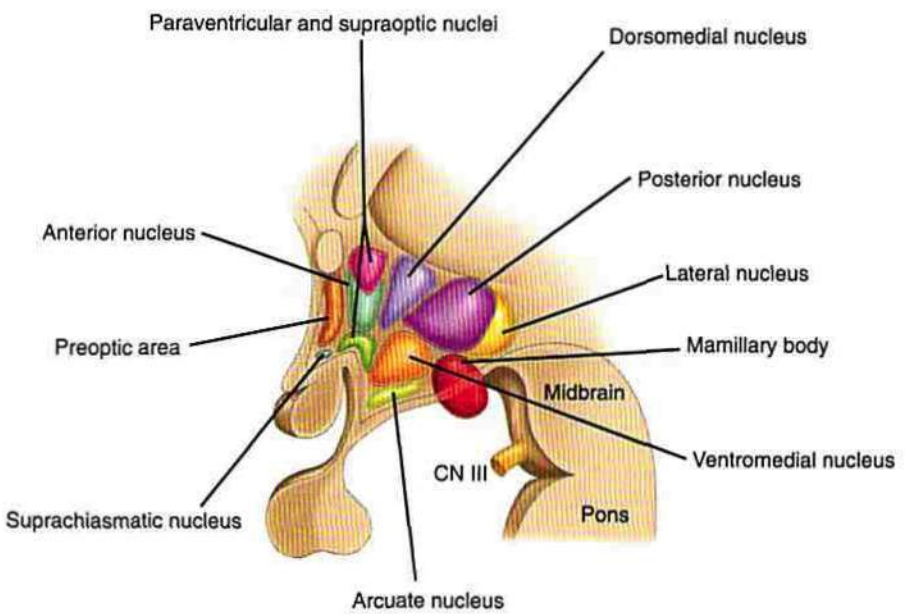


FIGURE 6-25. Hypothalamic nuclei.

TABLE 6-7. Hypothalamic Nuclei and Major Functions

Nucleus	Function
Supraoptic and paraventricular nuclei	Synthesizes ADH, oxytocin, CRH. Regulates water balance via ADH. Lesion → diabetes insipidus.
Anterior nucleus	Temperature regulation (heat dissipation). Lesion → hyperthermia. Stimulates parasympathetic nervous system.
Preoptic	Releases gonadotropic hormones. Sexual dimorphic nucleus: lesion → arrested sexual development, impotence, amenorrhea.
Suprachiasmatic nucleus	Regulates circadian rhythms.
Dorsomedial nucleus	Stimulation → obesity, disinhibition.
Posterior nucleus	Temperature regulation (heat conservation). Lesion → poikilothermia (poor thermoregulation). Stimulates sympathetic nervous system.
Lateral nucleus	Feeding center: Simulation → increased eating (lateral nucleus causes you to grow laterally) lesion → starvation.
Mamillary body	Damaged in Wernicke's encephalopathy (confabulation, amnsia). Hippocampus → fornix → mamillary body → anterior nucleus of thalamus.
Ventromedial nucleus	Satiety center: lesion → obesity, hyperphagia, "savage" behavior.
Arcuate nucleus	Produces hypothalamic releasing, inhibiting factors. Inhibits prolactin release via dopamine-/prolactin-inhibiting factor.

Diseases of the Hypothalamus

- Diabetes insipidus
  - Lesion of the antidiuretic hormone (ADH) pathways to the posterior lobe of the pituitary glands leads to inappropriately low ADH secretion.
  - Polyuria and polydipsia.
- Syndrome of inappropriate ADH secretion
  - Often due to lung tumors that secrete ADH-like hormone, or drugs that increase ADH secretion (carbamazepine, chlorpromazine).
  - Manifests as fluid retention with hyponatremia.
- Craniopharyngioma
  - Congenital tumor originating from remnants of Rathke's pouch.
  - Often calcified,
  - Most common supratentorial tumor and cause of hypopituitarism in children.
  - Pressure on the optic chiasm results in **bitemporal hemianopsia.**

KEY FACT

The pituitary gland or adenohypophysis is formed from an outpouching of the ectodermal diverticulum of the primitive mouth cavity, **Rathke's pouch.** The pouch ascends until it is adjacent to the neurohypophysis (a part of the hypothalamus), thus forming the adenohypophysis/neurohypophysis complex that rests in the **sella turcica.** Remnants of Rathke's pouch may give rise to a **craniopharyngioma.**

- Pressure on the hypothalamus results in hypothalamic syndrome (loss of function of the hypothalamus).
- Pituitary adenomas
  - Although not officially part of the hypothalamus, the pituitary is closely related both spatially and functionally.
  - Location of 15% of clinically symptomatic intracranial tumors.
  - Rarely seen in children (unlike craniopharyngiomas).
  - Produces symptoms similar to those of craniopharyngioma (bitemporal hemianopia and hypothalamic syndrome).
  - If endocrine-active, produce endocrine abnormalities (i.e., amenorrhea, galactorrhea from prolactin-secreting tumor).

CEREBELLUM

The cerebellum extends dorsally from the level of the pons at the base of the brain. Important structures include the **vermis,** situated medially, and the hemispheres on either side. It is divided into three lobes: the **anterior, posterior,** and **flocculonodular** (see Figure 6-26). Major functions include coordination of movement and posture. The hemispheres control purposeful limb movements, while the vermis controls axial posture. Lesions of the cerebellum result in dysdiadochokinesia, essential tremor, and ataxia.

Anatomy

- Peduncles
  - Superior cerebellar peduncle: Contains major output from the cerebellum, the **dentatothalamic** tract, and the major afferent pathway, the ventral **spinocerebellar tract.**
  - Middle cerebellar peduncle: Contains incoming pontocerebellar fibers.
  - Inferior cerebellar peduncle: Contains three major afferent tracts: the dorsal spinocerebellar tract, the cuneocerebellar tract, and the olivocerebellar tract from the contralateral inferior olivary nucleus.

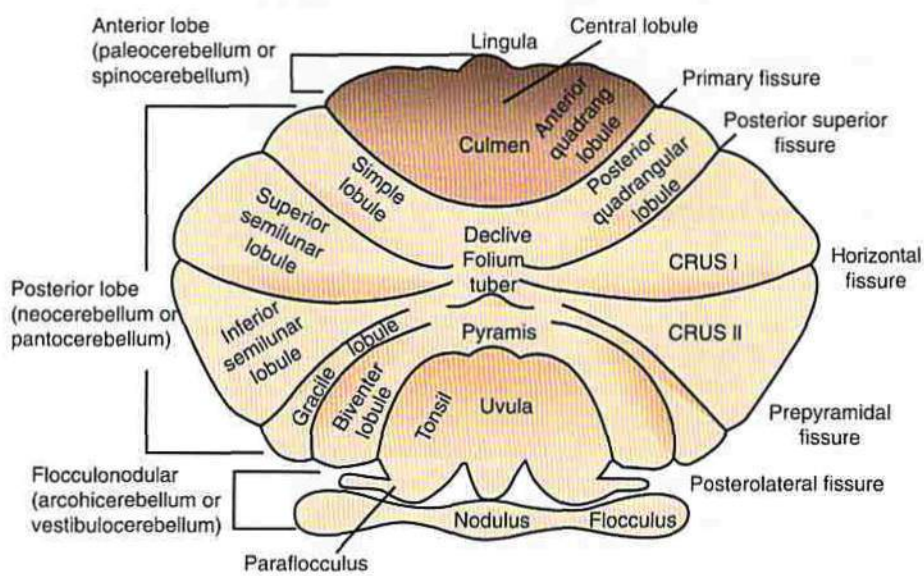


FIGURE 6-26. Lobes of the cerebellum. Anterior, posterior, and flocculonodular lobes. (Modified, with permission, from Ropper AH, Brown RH. *Adams and Victor's Neurology*, 8th ed, New York: McGraw-Hill, 2005: 71.)

- **Layers** (see Figure 6-27).
  - **Molecular layer:** Outer layer containing stellate cells, basket cells, and the dendritic arbor of Purkinje cells.
  - **Purkinje cell layer:** Contains cell bodies of Purkinje cells.
  - **Granule layer:** Innermost layer containing granule cells, Golgi cells, and cerebellar glomeruli.
  - **Cerebellar glomeruli:** Consists of a mossy fiber rosette, granule cell dendrites, and a Golgi cell axon.
- **Neurons and fibers** (see Table 6-8).

Major Pathways

- Climbing fibers of the inferior olive project via the olivocerebellar tract to the cerebellar cortex and synapse on Purkinje cells.
- Purkinje cells of the cortex project to the dentate nucleus.
- Dentate nucleus cells project via the dentatothalamic tract to the ventral lateral nucleus of the thalamus.

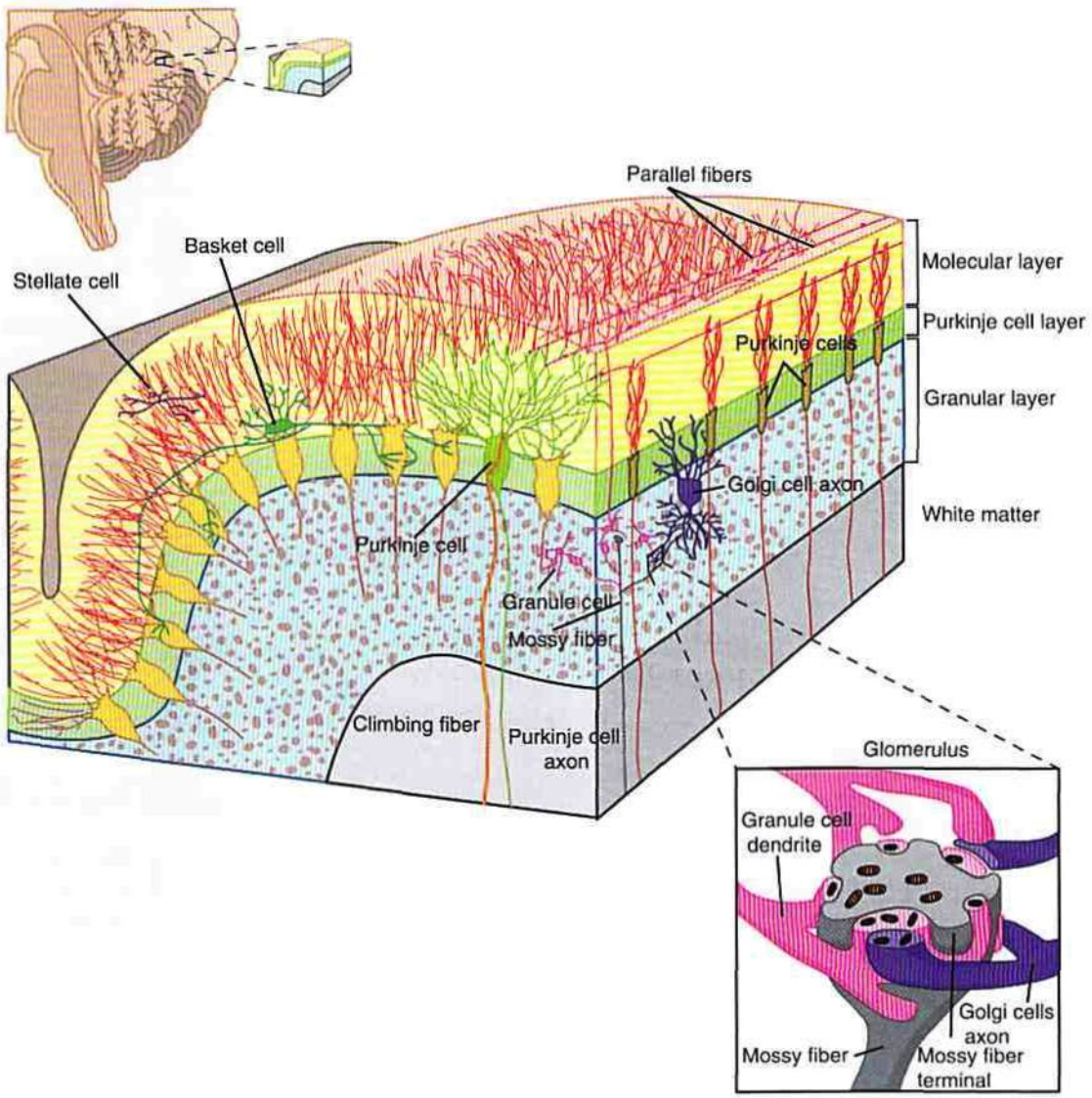


FIGURE 6-27. Histologic organization of the cerebellum. Purkinje cells have trees of dendrites that spread along a plane perpendicular to the parallel fibers, forming a matrix of information processing. (Modified, with permission, from Kandel ER, Schwartz JH, Jessel TM. *Principles of Neural Science*, 4th ed, New York: McGraw-Hill, 2000.)

TABLE 6-8. Neurons and Fibers of the Cerebellum

Cell/ Fiber	Location	Pathway	Neurotransmitter
Purkinje cells	Cell body in Purkinje cell layer; dendritic tree in molecular layer.	Only output from cerebellar cortex. Receives input from parallel and climbing fibers. Project to cerebellar and vestibular nuclei.	GABA
Granule cells	Cell body in granule cell layer; dendrites in molecular layer.	Receive input from Golgi cells and mossy fibers. Project to Purkinje, basket, stellate, and Golgi cells through parallel fibers.	Glutamate
Parallel fibers	Molecular layer.	Axons of granule cells.	Glutamate
Mossy fibers	Cell bodies are in spinal cord, pons, and vestibular nuclei; terminate in granule layer.	Originate in spinocerebellar, pontocerebellar, and vestibulocerebellar tracts. Terminate as mossy fibers on granule cells.	Glutamate
Climbing fibers	Cell bodies in inferior olivary nucleus; terminate in granule layer and molecular layer.	Carry information from olivocerebellar tract to cerebellar nuclei and Purkinje cells.	Aspartate

- Thalamic neurons project to the primary motor cortex.
- The motor cortex projects via the corticopontine tract and pontine nuclei.
- Pontine nuclei project via the pontocerebellar tract to the contralateral cerebellar cortex (mossy fibers).

Cerebellar Dysfunction and Syndromes

- Cerebellar signs include the triad of:
  1. **Hypotonia.**
  2. **Disequilibrium** (loss of balance, truncal and gait ataxia).
  3. **Dyssynergia** (loss of coordination) includes dysmetria, intention tremor, dysdiadochokinesia, and **coarse** nystagmus that worsens with gaze **toward** the side of the lesion.
- Lesions of the hemispheres usually cause ipsilateral cerebellar signs with ataxia of the extremities.
- Lesions of the vermis usually cause gait or truncal ataxia.

KEY FACT

Brain stem lesions produce a **Brown–Séquard–like syndrome**: Ipsilateral loss of some functions and contralateral loss of other functions. Many of the tracts that traverse to and from the brain and spinal cord synapse and cross the midline within the brain stem.

BRAIN STEM

The brain stem lies between the thalamus and the spinal cord. It develops from the mesencephalon (midbrain), the metencephalon (pons), and the myencephalon (medulla). It consists of three main components, in descending order: midbrain, pons, and medulla (see Figure 6-28).

Midbrain

The midbrain is the most superior aspect of the brain stem. It is important in several common syndromes that occur with strokes or other lesions in this area (see Figures 6-29 and 6-30 and Tables 6-9, 6-10, and 6-11).

- Blood supply: PCA.
- Consists of a dorsal tectum (roof), an intermediate tegmentum (floor), and a base.

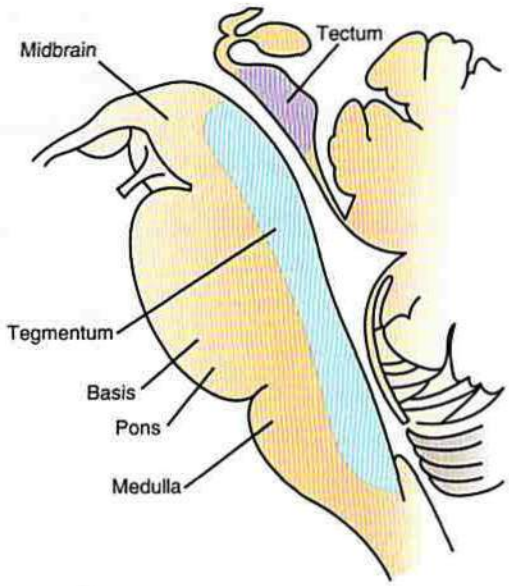


FIGURE 6-28. Brain stem. Basic parts of the brain stem include the midbrain, pons, and medulla. Tegmentum = "floor"; tectum = "roof." (Modified, with permission, from Waxman SG. *Clinical Neuroanatomy*, 25th ed, New York: McGraw-Hill, 2003.)

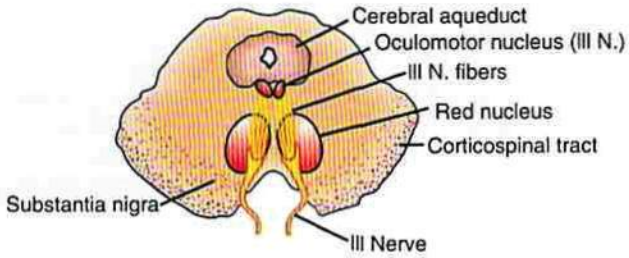


FIGURE 6-29. Cross-section of the midbrain. The tectum is above the aqueduct, the tegmentum below.

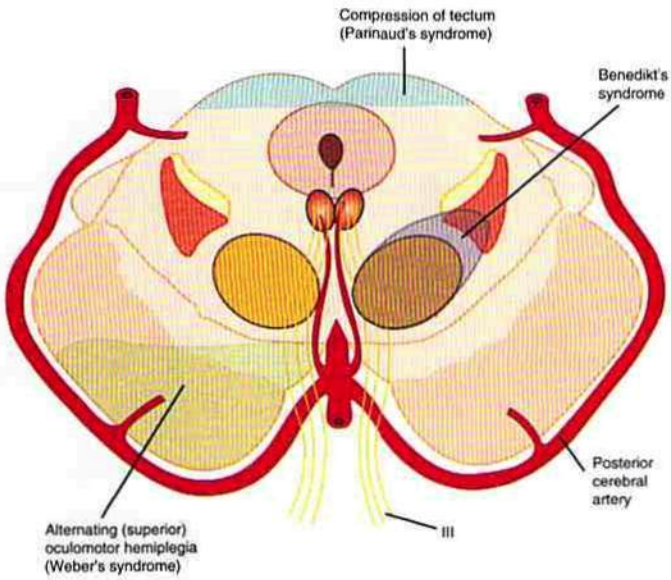


FIGURE 6-30. Lesions of the midbrain. Parinaud's, Benedikt's, and Weber's syndromes.

TABLE 6-9. Parinaud's Syndrome: Lesion of the Dorsal Tectum of the Midbrain

Structure	Deficit
Superior colliculus and pretectal area	Paralysis of upward and downward gaze, pupillary disturbances, absence of convergence.
Cerebral aqueduct	Obstruction leads to noncommunicating hydrocephalus.

Pons

The pons is the region of the brain stem shown in Figure 6-31.

- Blood supply: Paramedian branches of the basilar artery and anterior inferior cerebellar artery (AICA).
- Contents (see Table 6-12).

The pons contains an important structure for conjugate gaze, known as the **medial longitudinal fasciculus (MLF)**. The MLF connects the CN III nucleus with the contralateral CN VI nucleus to achieve lateral conjugate gaze. A lesion of the MLF produces **MLF syndrome** (internuclear ophthalmoplegia):

- Medial rectus palsy on attempted lateral conjugate gaze and nystagmus in the abducting eye.
- Often seen in **multiple sclerosis** (MS).

KEY FACT

Charcot's triad of MS includes:
1. Scanning speech
2. Intention tremor
3. Nystagmus (MLF syndrome; see above)

Caloric nystagmus is used to test brain stem function. Nystagmus has two phases: a slow phase in one direction (abnormal movement), followed by a fast phase (correcting movement) in the opposite direction. The direction of nystagmus is determined by the direction of the fast phase (see Figure 6-32).

KEY FACT

Key elements in control of gaze (see Figure 6-33). Frontal eye fields → pontine paramedian reticular formation → CN VI nucleus → lateral rectus and MLF → CN III nucleus → medial rectus. Any lesion along this path leads to failure of lateral conjugate gaze.

- Conscious:
  - Cold water irrigation of the external auditory meatus → nystagmus toward the opposite side.
  - Warm water irrigation of the external auditory meatus → nystagmus toward the same side.
- Unconscious with brain stem intact: Cold water irrigation leads to deviation of the eyes toward the same side.
- Bilateral MLF lesion: Cold water irrigation leads to deviation of only the ipsilateral eye toward the same side.
- Low brain stem lesion: No response.

TABLE 6-10. Benedikt's Syndrome: Lesion of the Tegmentum of the Midbrain

Structure	Deficit
CN III nucleus/root	Ptosis (paralysis of the levator palpebra muscle), fixed and dilated ipsilateral pupil, complete ipsilateral oculomotor paralysis, causing the eye to be "down and out" due to unopposed actions of the lateral rectus (CN VI) and superior oblique (CN IV) muscles.
Dentatothalamic fibers	Contralateral cerebellar dystaxia with intention tremor.
Medial lemniscus	Contralateral loss of tactile sensation from the extremities.

TABLE 6-11. Weber's Syndrome: Lesion of the Base of Midbrain

Structure	Deficit
CN III nucleus/root	See Table 6-9.
Corticospinal tracts	Contralateral spastic paralysis of extremities.
Corticobulbar fibers	Contralateral weakness of the lower face (CN VII), tongue (CN XII), and palate (CN X); the uvula is pulled toward the **normal side,** and the protruded tongue points to the **weak side.**

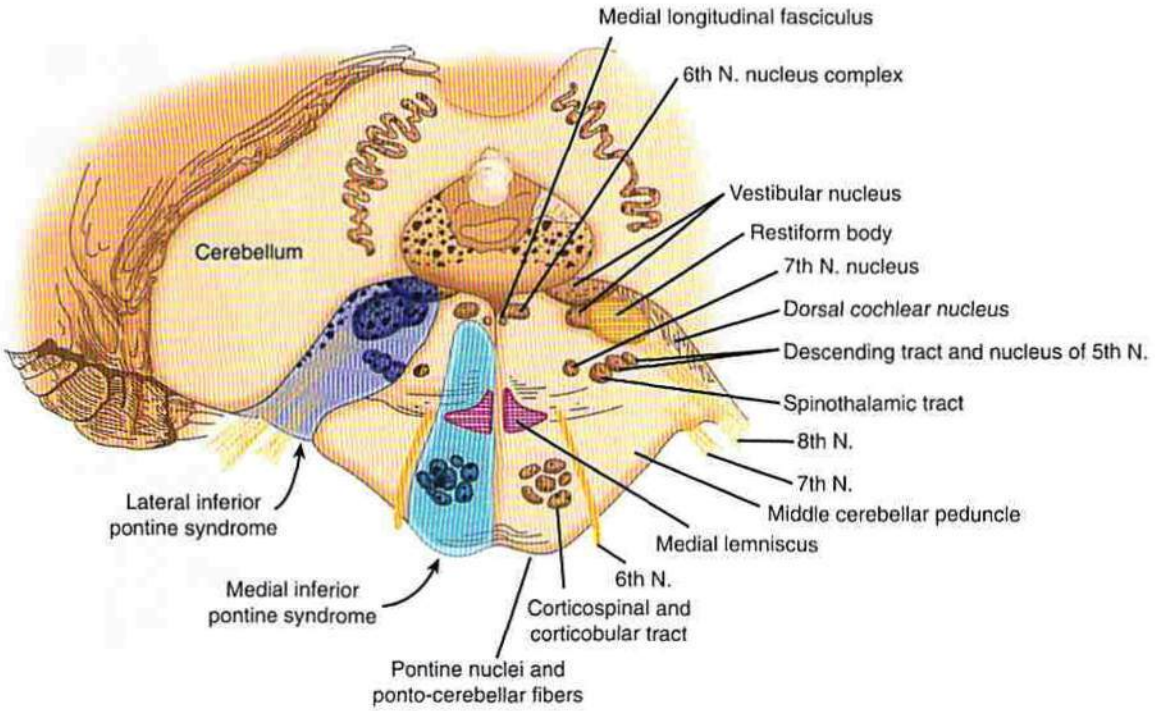


FIGURE 6-31. Cross-section through the pons. Note the regions of the lateral inferior pontine syndrome and medial inferior pontine syndrome due to occlusions of the anterior inferior cerebellar artery and the paramedian branch of the basilar artery. (Modified, with permission, from Ropper AH, Brown RH. *Adams and Victor's Neurology*, 8th ed, New York: McGraw-Hill, 2005: 683.)

TABLE 6-12. Contents and Lesions of the Medial Pons (Result From Occlusion of Paramedian Branches of the Basilar Artery)

Structure	Deficit
Medial longitudinal fasciculus	Medial longitudinal fasciculus (MLF) syndrome (see below).
Abducent nucleus (CN VI)	Lateral rectus palsy.
CN VII (lower motor neuron)	Bell's palsy without forehead sparing.
Medial lemniscus	Loss of facial pain and temperature sensation.
Corticospinal tract	Hemiparesis.

MNEMONIC

Remember the direction of nystagmus with **COWS.**

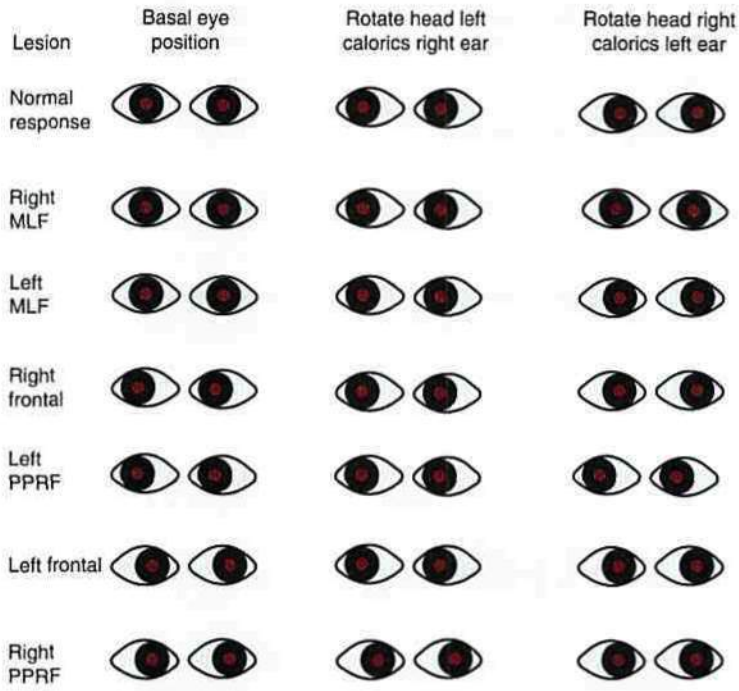


FIGURE 6-32. Responses to cold caloric testing in brain stem injury. PPRF = pontine paramedian reticular formation; MLF= medial longitudinal fasciculus.

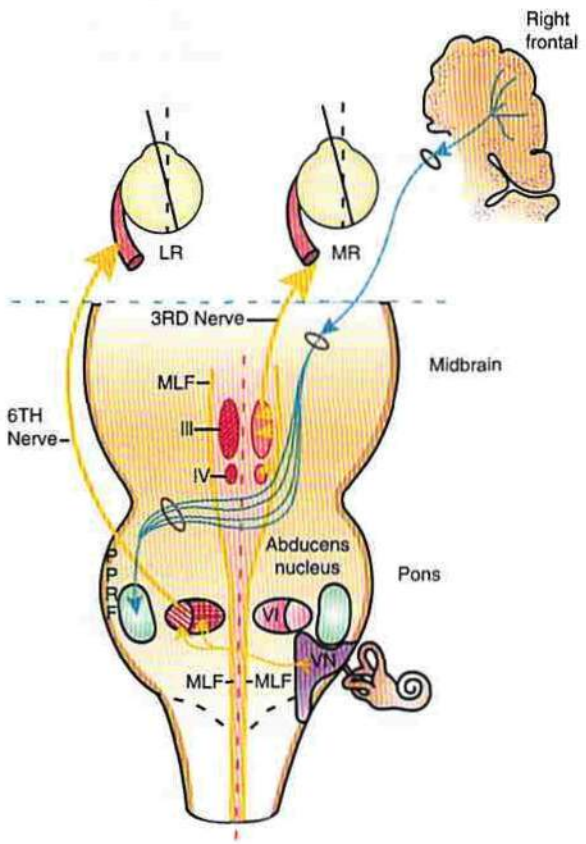


FIGURE 6-33. Elements of control of lateral conjugate gaze. LR = Lateral rectus; MLF = medial longitudinal fasciculus; MR = MEDIAL RECTUS; VN = vestibular nuclei.

- Other important clinical correlations:
  - Acoustic neuroma (schwannoma): Benign tumor of the Schwann cells of CN VIII that arises in the area of the internal auditory meatus and cerebellopontine angle. Seen in neurofibromatosis II (NF II).
    - CN VIII → tinnitus, unilateral nerve deafness, vertigo, nystagmus, nausea, vomiting, unsteady gait (see Table 6-13).
    - CN VII → ipsilateral facial weakness and loss of corneal reflex (efferent limb).
    - CN V → paresthesias, anesthesia of the ipsilateral face, loss of corneal reflex (afferent limb).
  - **"Locked-in" syndrome:** Lesion of the base of the pons from infarction, trauma, tumor, or demyelination.
    - Affects bilateral corticospinal and corticobulbar tracts → complete paralysis from head to toe.
    - Spares the oculomotor and trochlear nerves → patient only able to communicate with vertical eye movements.
  - **Central pontine myelinolysis:** Lesion of the base of the pons, associated with alcoholism or rapid correction of hyponatremia.
    - Affects the corticospinal and corticobulbar tracts → spastic quadriparesis, pseudobulbar palsy, mental changes; may progress to "locked-in" syndrome.

Medulla

- Blood supply: Anterior spinal artery, posterior inferior cerebellar artery (PICA).
- Contents are shown in Figure 6-34.
- Lesions result in important clinical syndromes (see Tables 6-14 and 6-15). Wallenberg syndrome is particularly common as a result of either stroke in PICA or vertebral arteries.

Other functions of the medulla include:

- Vomiting center: Neurons at the base of the fourth ventricle sample CSF and send inputs to the vomiting center.
- Respiratory regulation: At low blood pH, receptors in the medulla activate the **reticular formation** (a diffuse group of neurons controlling vital functions) within the medulla. The phrenic nerve is then activated via CN IX and X, stimulating contraction of the diaphragm.
  - Lesion → respiratory depression, decreased response to hypercapnia.
- Consciousness: Disruption of the reticular formation secondary to lesions or alterations in neurotransmitters may lead to changes in consciousness (i.e., coma) and even death. Injuries of the reticular formation may result from neck trauma, tumor, and cerebellar herniation due to increased ICP.

TABLE 6-13. Medial Medullary Syndrome

Structure	Deficit
Corticospinal tract	Contralateral spastic hemiparesis.
Medial lemniscus	Contralateral loss of tactile and vibration sense from trunk and extremities.
CN XII nucleus/fibers	Ipsilateral flaccid hemiparalysis of the tongue (tongue points to side of lesion).



MNEMONIC

The cerebellopontine angle is the angle formed by the cerebellum, pons, and medulla. Five brain tumors are often found here (SAMEE):

Schwannoma
Arachnoid cyst
Meningioma
Epependymoma
Epidermoid

KEY FACT

NF II often occurs with **bilateral** acoustic neuromas.

KEY FACT

The medulla is the level at which the corticospinal tract crosses the midline (decussates). The crossing fibers of the corticospinal tract comprise the **pyramidal decussation.**

KEY FACT

Horner's syndrome:
- Ptosis
- Miosis
- Hemianhidrosis (lack of sweating)
- Apparent enophthalmos (sunken eyeball)

FLASH FORWARD

Causes of Horner's syndrome include Pancoast tumor, carotid artery dissection, and upper brachial plexus injury.

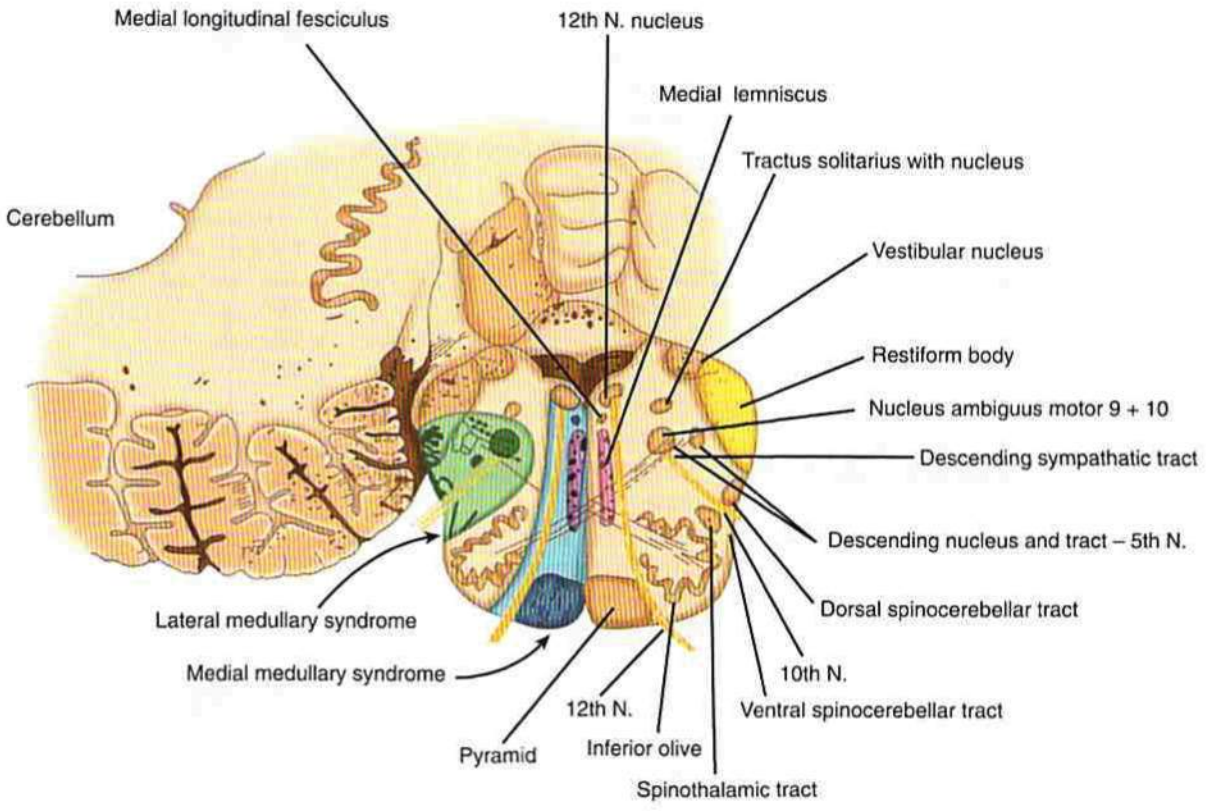


FIGURE 6-34. Cross-section through the medulla. Note the regions involved in the lateral medullary syndrome and medial medullary syndrome due to occlusion of the posterior inferior cerebellar artery and anterior spinal artery. (Modified, with permission, from Ropper AH, Brown RH. *Adams and Victor's Neurology*, 8th ed, New York: McGraw-Hill, 2005: 678.)

- BP regulation: Receptors in the medulla, the carotid bodies, and the aorta sense stretching of the vessel and send signals to the medulla to increase or decrease BP as needed,
  - Lesion → hypotension, orthopnea.

NEUROTRANSMITTERS

Several important neurotransmitters have unique functions in the brain. They are associated with certain groups of cells that control their release, where they are found in high concentrations (see Table 6-16).

TABLE 6-14. Lateral Inferior Pontine Syndrome (Result of Anterior Inferior Cerebellar Artery Occlusion)

STRUCTURE	DEFICIT
Lateral spinothalamic tract	Loss of contralateral pain and temperature sensation.
CN VIII nuclei	Vertigo, hearing loss, tinnitus.
CN VII	Bell's palsy without forehead sparing.

TABLE 6-15. Lateral Medullary/Wallenberg's/Posterior Inferior Cerebellar Artery Syndrome

Structure	Deficit
Vestibular nuclei	Nystagmus, vertigo.
Inferior cerebellar peduncle	Ipsilateral cerebellar signs.
Nucleus ambiguus	Dysarthria, hoarseness, dysphagia, loss of gag reflex.
Spinothalamic tracts/spinal trigeminal nucleus	**Contralateral** loss of pain and temperature sensation from trunk and extremities, with **ipsilateral** loss of pain and temperature sensation in the face.
Descending sympathetic tract	Ipsilateral Horner's syndrome.

SPINAL CORD

The spinal cord continues caudally from the brain stem as a long cord-like structure which gives off branches along the length of the spine.

Blood Supply

Anterior (1) and posterior (2) spinal arteries.

Function

The spinal cord carries information from the brain and brain stem to different parts of the body.

TABLE 6-16. Neurotransmitters of the Nervous System

Neurotransmitter	Acetylcholine	Dopamine	Norepinephrine	Serotonin
Functions	Peripheral nervous system.	Movement.	Anxiety, panic attacks.	Depression.
	Neuromuscular junction.	Reward pathway.	Mood disorders.	
	Parasympathetic nervous system.	Controls release of prolactin.		
	Preganglionic sympathetic fibers.			
	Postganglionic sympathetic fibers of sweat glands and blood vessels.			
Major sites in the brain	Nucleus basalis of Meynert (degenerates in Alzheimer's disease).	Substantia nigra of midbrain (degenerates in Parkinson's disease).	Locus ceruleus of pons and midbrain.	Raphe nucleus of the brain stem.
	Caudate and putamen (degenerates in Huntington's disease).	Arcuate nucleus of hypothalamus.		

Levels of the Spinal Cord

In the cervical region, the spinal cord level shares the same number as the spinal segment **below** it. In other spinal regions, however, it shares the same number as the spinal segment **above** it. Each segment receives sensory input from dermatomal regions of the body and sends motor output to myotomal regions (see Figure 6-35 and Table 6-17).

- Cervical (C1–C8)
- Thoracic (T1–T12)
- Lumbar (L1–L5)
- Sacral (S1–S5)
- Coccygeal

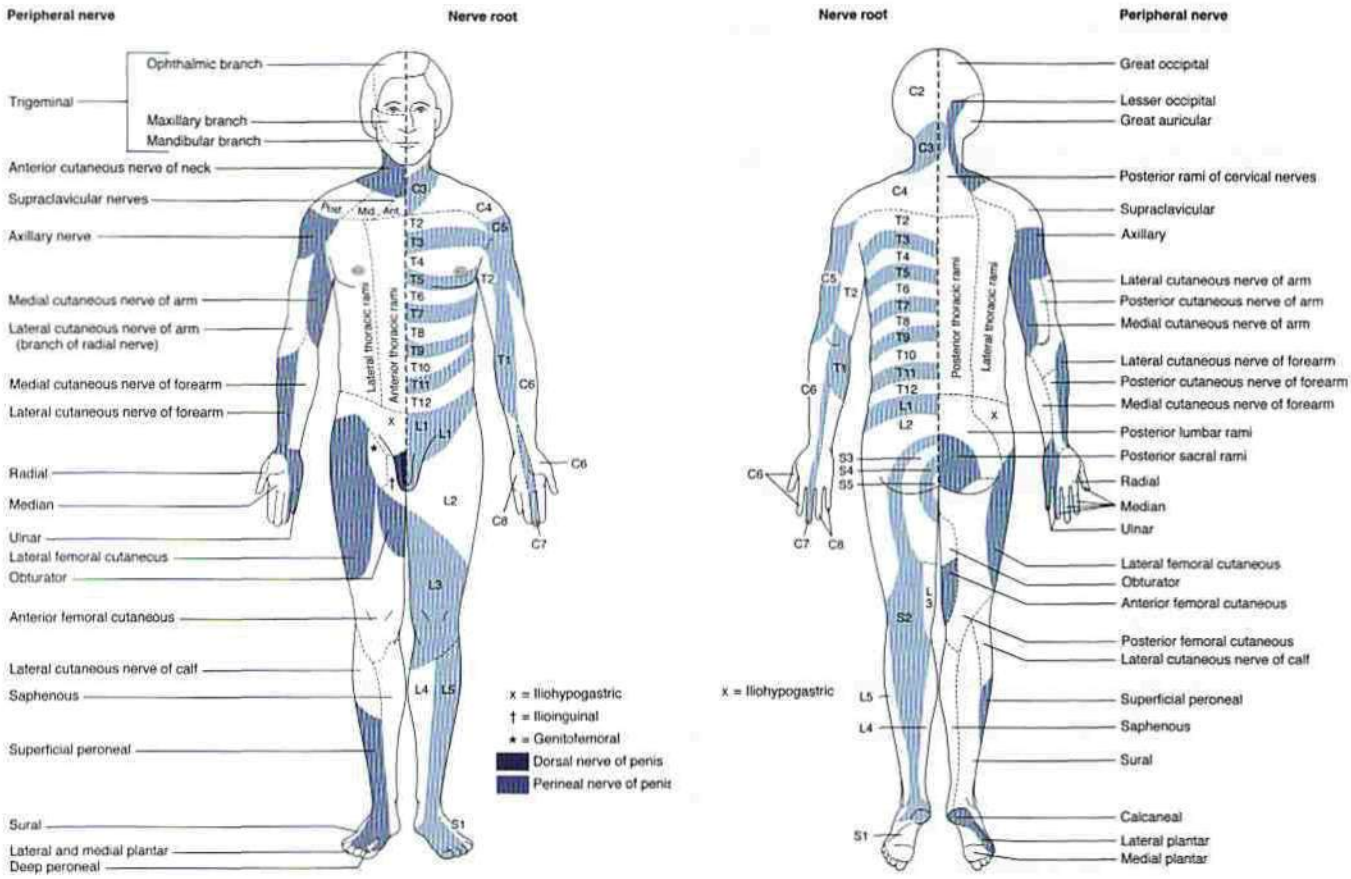


FIGURE 6-35. Cutaneous innervation (anterior and posterior views). (A) Cutaneous innervation (anterior view). The segmental or radicular (nerve root) distribution is shown on the left side of the body, and the peripheral nerve distribution on the right side of the body. (B) Cutaneous innervation (posterior view). The segmental or radicular (nerve root) distribution is shown on the left side of the body, and the peripheral nerve distribution on the right side of the body.

TABLE 6-17. Major Motor and Sensory Nuclei

Name	Segment	Function
Ciliospinal center of Budge	C8–T2	SNS innervation of the eye
Intermediolateral cell column	C8–L3	SNS innervation of the body
Nucleus dorsalis of Clark	C8–L3	Dorsal spinocerebellar tract
PNS nucleus	S2–S4	Sexual, urination, defecation
Spinal accessory nucleus	C1–C6	CN XI functions
Phrenic nucleus	C3–C6	Diaphragmatic movement

KEY FACT

Cauda equina = "tail of the horse"

KEY FACT

During growth, the spinal column elongates much more than does the spinal cord within it. Thus, the spinal cord terminates at a more cranial level in adults than in newborns.

Unique Structures

- **Cauda equina:** At the caudal end, the spinal cord splits into multiple separate motor and sensory roots, called the cauda equina, which exits the vertebral canal through the lumbar intervertebral and sacral foramina.
- **Conus medullaris:** The median cord remaining in the spine following the deviation of the cauda equina. Terminates at L3 in newborns and at the lower border of L1 in adults (see Figure 6-36).

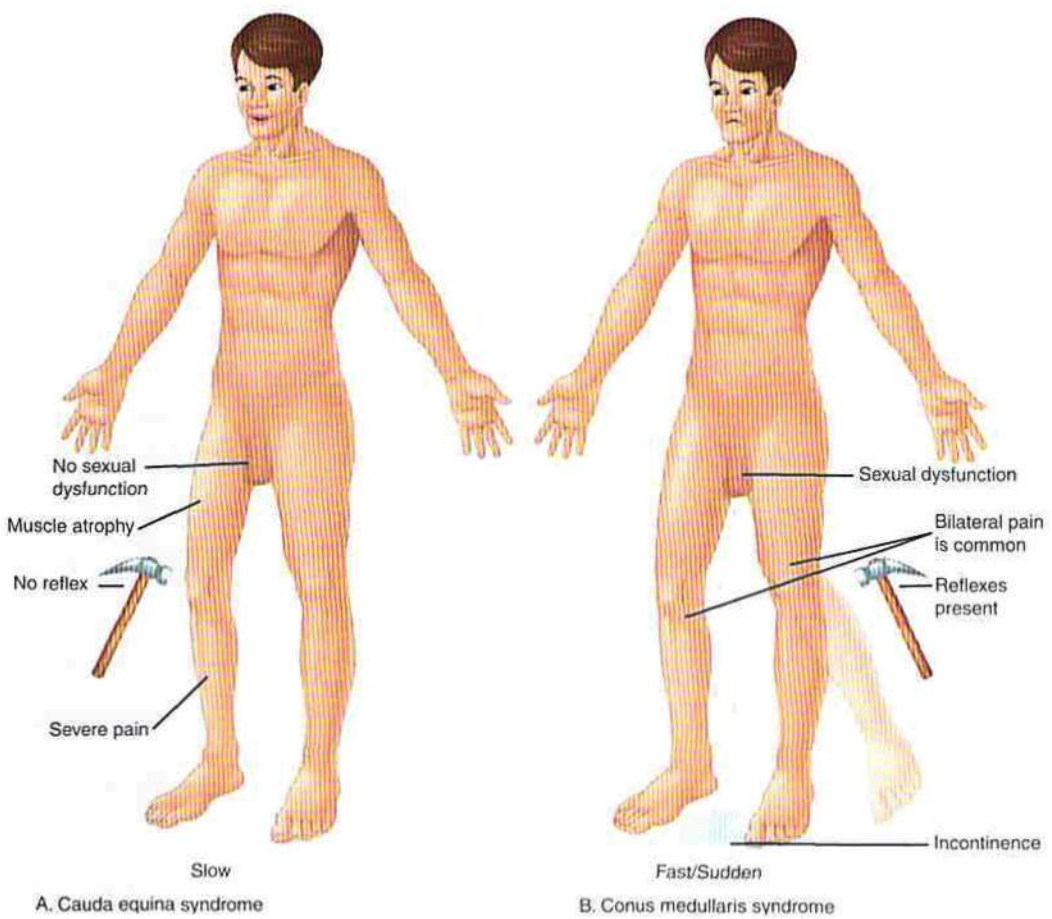


FIGURE 6-36. Cauda equina versus conus medullaris syndrome. (A) Cauda equina syndrome is characterized by preservation of sexual function, muscle atrophy, unilateral pain and areflexia, and a slow progression. (B) Conus medullaris syndrome is characterized by sexual dysfunction, bilateral mild pain, incontinence, and preservation of reflexes.

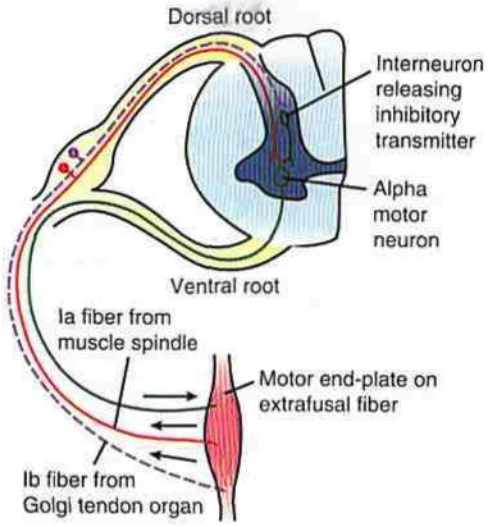


FIGURE 6-37. Myotatic reflex pathway. Diagram of the myotatic/stretch reflex. The Ib Golgi tendon organ fiber transmits information about tension in the tendon. (Modified, with permission, from Waxman SG. *Clinical Neuroanatomy*, 25th ed, New York: McGraw-Hill, 2003.)

Myotatic Reflex

The myotatic reflexes are monosynaptic, ipsilateral **muscle stretch reflexes**, also known as deep tendon reflexes. Interruption of either the afferent or efferent limb results in **areflexia.** The pathway of the myotatic reflex is as follows (see Figure 6-37):

- Afferent limb: Muscle spindle (receptor) → dorsal root ganglion neuron → Ia fiber.
- Efferent limb: Ventral horn motor neuron → striated muscle (effector).

Reflexes and Corresponding Levels

Reflexes are used to test the integrity of the spinal cord at their corresponding levels (see Table 6-18).

Cross-Section of the Spinal Cord

- Gray matter: Central "butterfly" that contains the cell bodies of neurons that send projections either to the periphery or up through the spinal cord tracts.
- White matter: Myelinated tracts of the spinal cord.

TABLE 6-18. Deep Tendon Reflexes

Muscle Stretch Reflex	Cord Segment	Muscle
Ankle jerk	S1	Gastrocnemius
Knee jerk	L2–L4	Quadriceps
Biceps jerk	C5–C6	Biceps
Forearm jerk	C5–C6	Brachioradialis
Triceps jerk	C7–C8	Triceps

- Gray communicating rami: Contain unmyelinated postganglionic sympathetic fibers.
- White communicating rami: Contain myelinated preganglionic sympathetic fibers. Found only from T1 to L3 in conjunction with the lateral horn and intermediolateral cell column.
- White vs. gray matter mass throughout the spinal cord:
  - The ratio of gray:white matter in the cross-section of the cord increases as you travel down the spinal cord.

FLASH BACK

The **intermediolateral cell column** contains neuron cell bodies for the entire sympathetic system. It appears as the **lateral horn** jutting out of the butterfly from C8 to L3. Fibers arising from the intermediolateral cell column then exit the spinal cord via the **white communicating rami** from segments T1 to L3.

Tracts of the Spinal Cord

The spinal cord is similar to a bundle of electrical wires with various types of information traveling along their respective paths (see Figure 6-38).

- **Motor** pathways travel **away** from the brain. The names of motor pathways begin with the brain structure and end with **-spinal** (i.e., rubro**spinal** tract).
- **Sensory** pathways travel **toward** the brain. The names of sensory pathways begin with **spino-** and end with the brain structure (i.e., **spino**thalamic tract).

Corticospinal Tracts

The major motor tracts from the cortex. Conduct signals directing purposeful actions (see Figure 6-39).

- Lateral corticospinal tract: Mediates voluntary skilled motor activity, primarily of the upper limbs.
  - Origin: Cell bodies are the **giant cells of Betz** in layer V of the cortex (see Figure 6-39).
    - Premotor cortex (Brodmann's area 6).
    - Primary motor cortex (Brodmann's area 4).
    - Primary sensory cortex (Brodmann's areas 1, 2, and 3).
  - Course:
    - Cortex: The axons of the cells of Betz pass through the brain as the posterior limb of the internal capsule, which then forms the crus cerebri as it enters the midbrain.

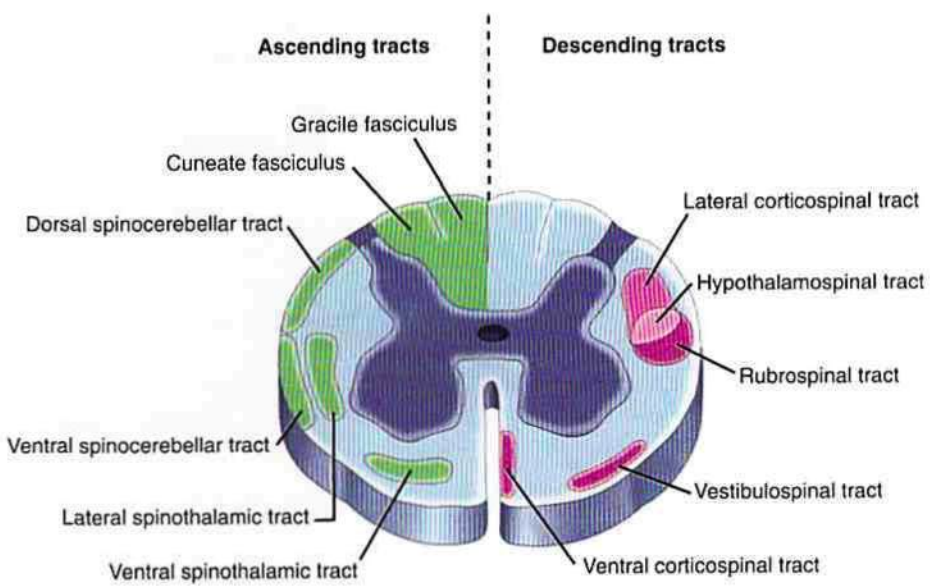


FIGURE 6-38. Tracts of the spinal cord.

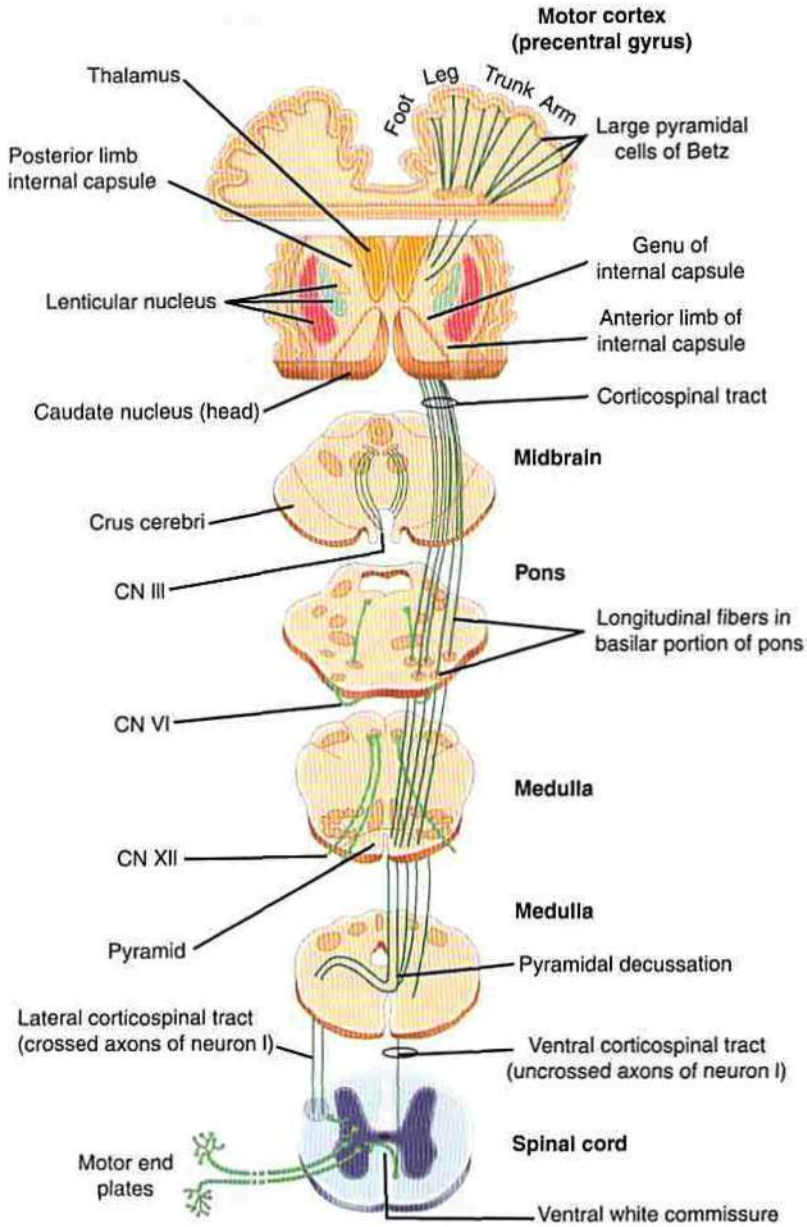


FIGURE 6-39. Lateral and ventral corticospinal tracts. The ventral and lateral tracts deviate from each other at the level of the medulla.

KEY FACT

Before the decussation, the lateral and anterior corticospinal tracts run together. At the decussation of the pyramids in the medulla, 85%–90% of corticospinal fibers decussate and form the **lateral corticospinal tract,** while the remaining 10%–15% continue as the **ventral corticospinal tract**.

KEY FACT

The lateral corticospinal tract inhibits the **Babinski reflex** (extension of the big toe and flexion of the remaining toes). Because myelination of the lateral corticospinal tract is notcomplete until the second year of life, children < 2 years old have a positive Babinski's sign. Any **UMN lesion** or lesion of the tract above the alpha motor neuron synapse (i.e., spinal cord, cortex) also results in a positive Babinski's sign.

- Brain stem: The fibers continue through the brain stem and decussate in the medulla, forming the medullary "pyramids."
- Spinal cord: The axons travel along the corticospinal tract in the lateral aspects of the spinal cord.

- Termination: The fibers synapse onto interneurons within the adjacent gray matter, which then synapse onto alpha motor neurons within the ventral horn of the spinal cord.
- Transection:
  - Above the decussation, injury results in **contralateral spastic paresis and Babinski's sign.**
  - In the spinal cord, transection results in **ipsilateral spastic paresis and Babinski's sign.**

- Ventral corticospinal tract: Mediates posture and gross movements involving the neck and trunk and lower limbs.
  - Origin: Premotor cortex (Brodmann's area 6).
  - Course: Same as that of the lateral corticospinal tract **until the decussation of the pyramids** in the **medulla,** where the ventral corticospinal tract does not decussate and continues ipsilaterally along the ventral white matter of the spinal cord.
  - Termination: The fibers then terminate **bilaterally** near the level of exit of the corresponding alpha motor neurons. Decussating fibers form the **ventral white commissure.** Axons then synapse on alpha motor neurons in the ventral horn of the ipsilateral and contralateral spinal cord. These motor neurons innervate axial muscles used in balance and posture.
  - Transection → axial/truncal instability (transaction in the brain stem and spinal cord have the same manifestation because this tract is uncrossed). Unilateral transection results in more subtle defects because the axial muscles have bilateral innervation.
- Hypothalamospinal tract: Carries autonomic information from the hypothalamus.
  - Origin: Hypothalamus.
  - Course: Travels from the hypothalamus through the lateral tegmentum of the brain stem and down through the dorsolateral quadrant of the lateral funiculus.
  - Termination: Ciliospinal center of the intermediolateral cell column at T1–T2.
  - Transection → **Horner's syndrome:** Ipsilateral miosis, ptosis, hemianhidrosis, and apparent enophthalmos.
- Other motor tracts: Mediate coordination of movements and balance. The specific functions are beyond the scope of Step 1.
  - Vestibulospinal tract
  - Rubrospinal tract
- **Sensory** pathways
  - Sensory receptors: Pacinian corpuscles, Meissner's corpuscles, joint capsule receptors, muscle spindles, Golgi tendon organs.
  - First-order neurons: Cell bodies are located in the dorsal root ganglia. Dendrites terminate as receptors in the periphery. Axons project to the spinal cord and give rise to the following:
    - The **gracile fasciculus** arises from sensory axons from the lower extremities. Ascends the spinal cord and synapses on the gracile nucleus.
    - The **cuneate fasciculus** arises from sensory axons from the upper extremity. Ascends the spinal cord and synapses on the cuneate nucleus.
  - Dorsal column–medial lemniscus pathway: Mediates tactile discrimination, vibration sensation, form recognition, and conscious proprioception (joint and muscle sensation; see Figure 6-40).
    - Spinal reflex collaterals that branch off the main axon and synapse on 1a fibers (see "myotatic reflex").
  - Second-order neurons:
    - Cell bodies: Gracile and cuneate nuclei of the caudal medulla.
    - Axons: Decussate as **internal arcuate fibers**, form the **medial lemniscus**, and then ascend the contralateral brain stem.
    - Termination: Synapse on neurons of the **ventroosterolateral (VPL) nucleus** of the thalamus.
  - Third-order neurons: Located in the VPL nucleus of the thalamus. Axons project through the posterior limb of the internal capsule to the

KEY FACT

Since the **cuneate fasciculus** carries sensory axons from the upper extremity to the spinal cord, it does not exist below T2, the most *inferior level of nerves supplying the* upper extremity.

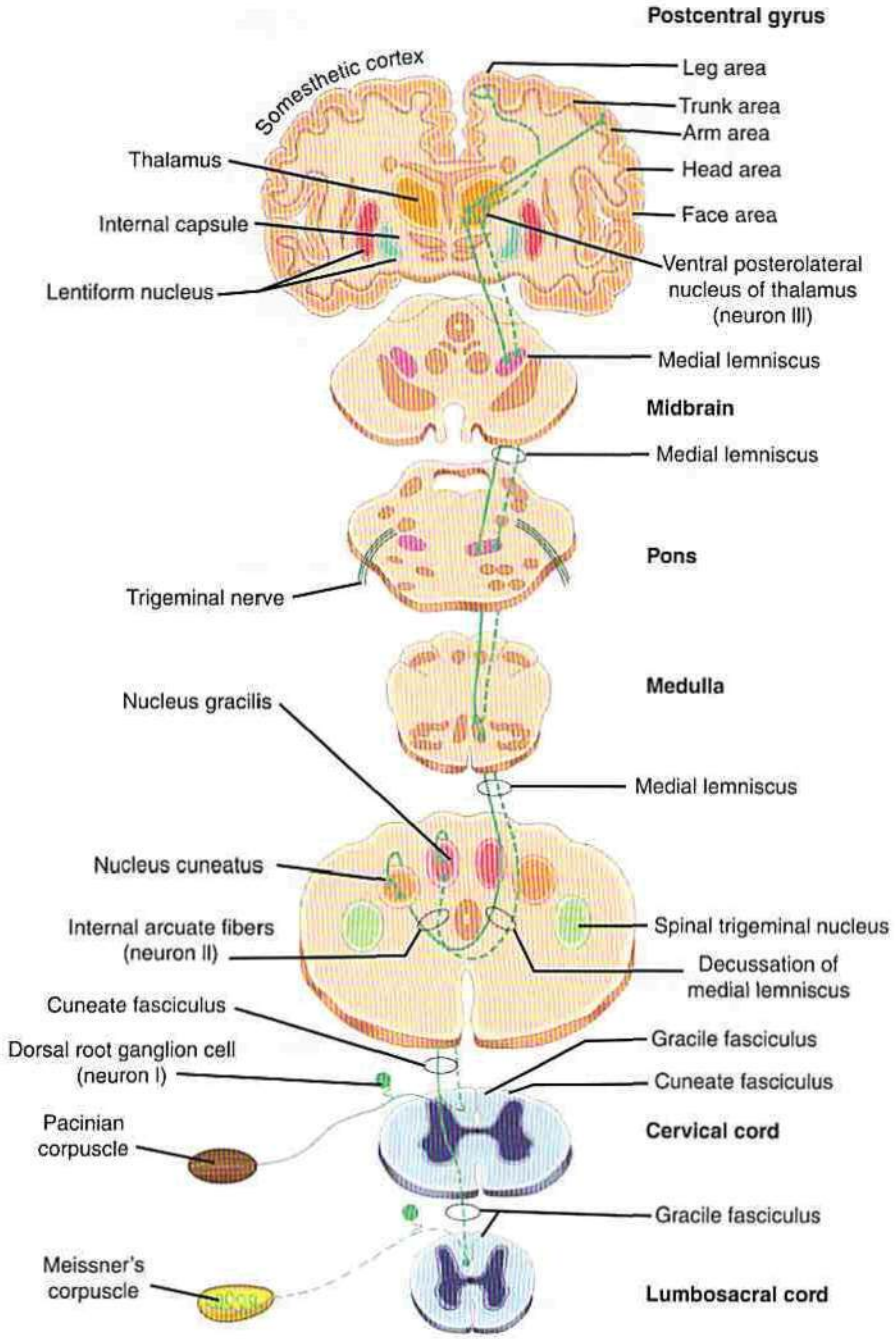


FIGURE 6-40. Dorsal column–medial lemniscus pathway. Impulses from light touch, pressure, and vibration travel along this pathway.

primary somatosensory cortex (Brodmann's areas 1, 2, 3) in the postcentral gyrus.

- Transection
  - **Above the decussation** of the internal arcuate fibers → **contralateral** loss of fine touch, vibration, and proprioception.
  - In the **spinal cord** → **ipsilateral** loss of modalities.

- Lateral spinothalamic tract: Mediates pain and temperature sensations (see Figure 6-41).
  - Receptors: Free nerve endings divided into **fast** and **slow conducting pain fibers** (A and C fibers, respectively).

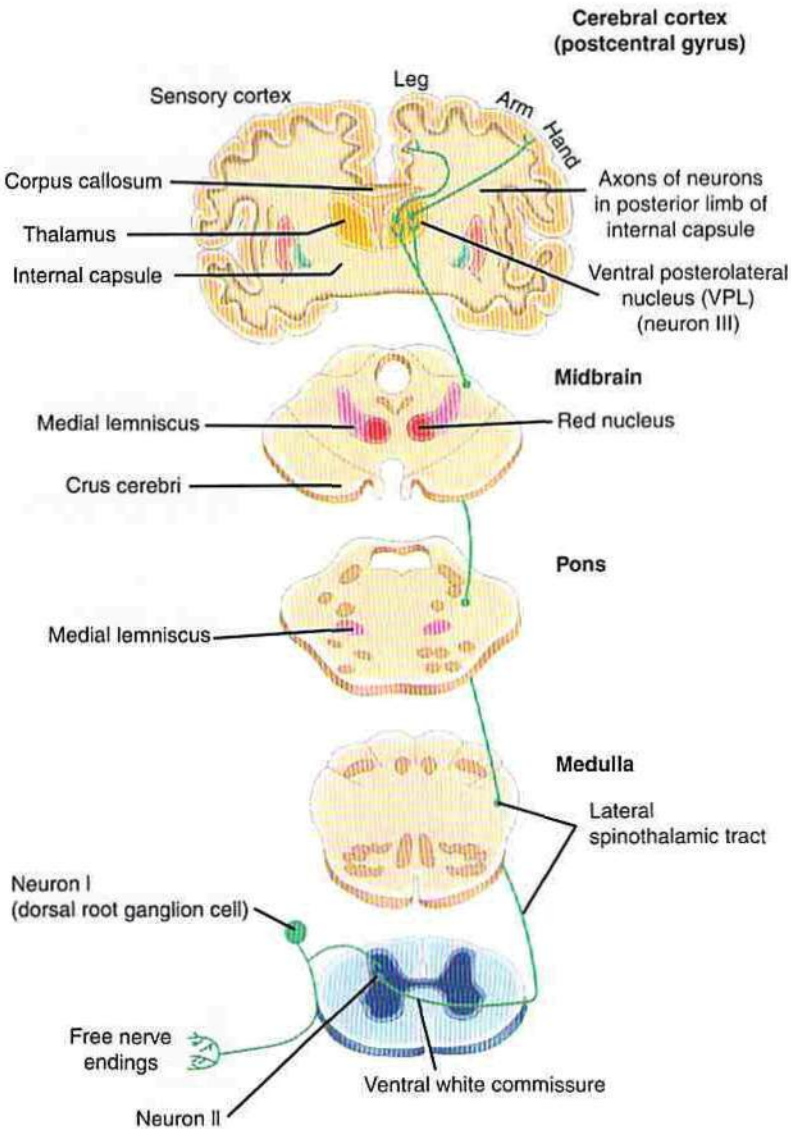


FIGURE 6-41. Spinothalamic tract.

- First-order neurons: Cell bodies are found in the dorsal root ganglia. Dendrites terminate as free nerve endings. Axons project to the spinal cord and ascend or descend a few levels within the **tract of Lissauer (lateral root entry zone)** before synapsing ipsilaterally on second-order neurons.
- Second-order neurons: Cell bodies are found in the dorsal horn. Axons decussate in the **ventral white commissure** and ascend in the contralateral **lateral funiculus.** Axons terminate in the VPL nucleus of the thalamus.
- Third-order neurons: Like those of the dorsal column-medial lemniscus tract, third-order neurons are located in the VPL nucleus of the thalamus. Axons project through the posterior limb of the internal capsule to the **primary somatosensory cortex** (Brodmann's areas 3–1–2) in the postcentral gyrus.
- Transection → **contralateral** loss of pain and temperature sensation **below** the lesion.

KEY FACT

Both the dorsal column–medial lemniscus and the spinothalamic tract follow the same rule: Primary afferents synapse ipsilaterally, and then secondary afferents synapse, then cross. The decussations just occur at different levels.

KEY FACT

Fasciculations are coordinated spontaneous depolarizations of a group of muscle fibers that are innervated by one motor neuron.
Fibrillations are small spontaneous depolarizations of a single muscle fiber that has been denervated,

KEY FACT

Romberg's sign is a test for proprioception. The patient stands with feet together and closes the eyes. The examiner then gives the patient a gentle push forward. The sign is positive if the patient falls or loses balance.

FLASH BACK

The **nucleus pulposus** is the remnant of the notochord.

MNEMONIC

Divisions of CN V exit owing to **S**tanding **R**oom **O**nly.
CN V1: **Superior** orbital fissure
CN V2: Foramen **Rotundum**
CN V3: Foramen **Ovale**

Brown–Séquard Syndrome

Hemisection of the spinal cord or the brain stem results in Brown-Séquard syndrome. The first-order neurons of the lateral spinothalamic tract, carrying **ipsilateral** pain and temperature sensation, traverse within **Lissauer's tract** a few levels up or down the spinal cord before synapsing on second-order neurons. Therefore, if the lesion of the spinal cord involves Lissauer's tract (i.e., in a complete hemisection), there will be **ipsilateral** loss of pain and temperature sensation within two levels of the lesion, as well as **contralateral** loss of pain and temperature sensation below the lesion (see Figure 6-42).

Lesions of the Spinal Cord

These result in various symptoms, depending upon which tracts are affected (see Table 6-19 and Figures 6-43 and 6-44).

CRANIAL NERVES

Twelve cranial nerves innervate the head and neck. Symptoms of lesions of the cranial nerves are important in localizing pathology within the complex anatomy of the head and neck (see Figures 6-45 and 6-46 and Tables 6-20 and 6-21).

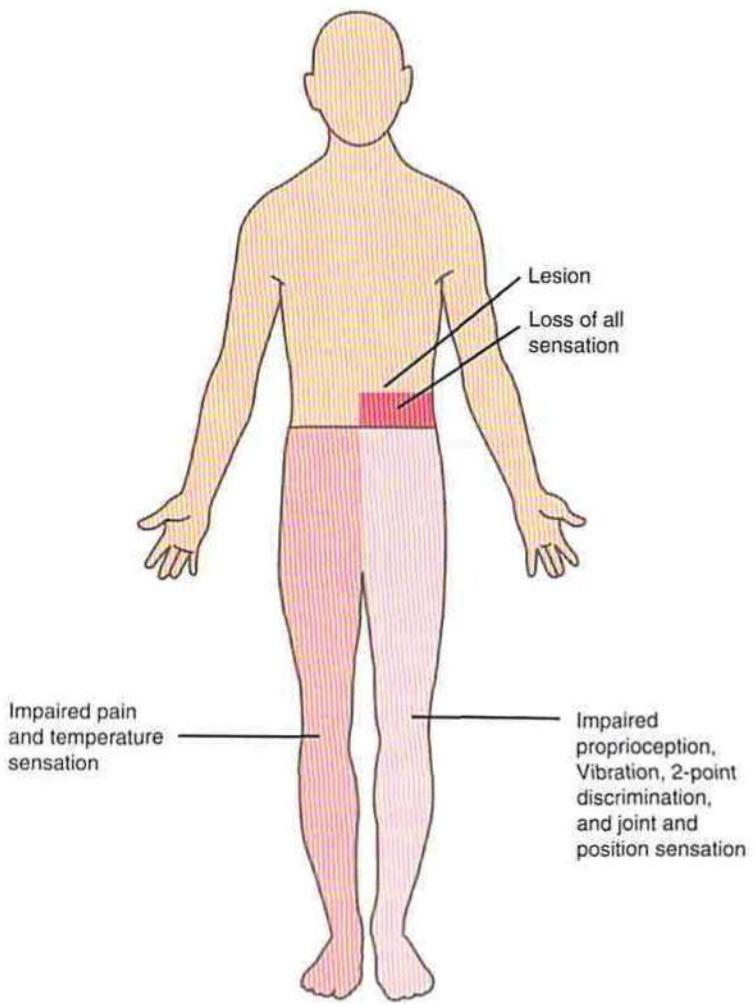


FIGURE 6-42. Brown-Séquard syndrome. (Modified, with permission, from Waxman SG. *Clinical Neuroanatomy*, 25th ed, New York: McGraw-Hill, 2003.)

TABLE 6-19. Lesions of the Spinal Cord

Category	Lesion	Mechanism	Clinical Manifestation	Examples/Other Facts
Motor pathway lesions	Upper motor neuron (UMN)	Transection of or damage to the corticospinal tract or cortical motor cells.	Spastic paresis with Babinski's sign.	Stroke, ischemic/traumatic injury to brain stem or spinal cord.
	Lower motor neuron (LMN)	Damage to motor neurons.	Flaccid paralysis, areflexia, atrophy, fasciculations, and fibrillations of the muscle fibers.	Poliomyelitis, Werdnig-Hoffman disease ("floppy baby"), tongue fasciculations, 7-month survival.
	Combined UMN and LMN	Damage to both corticospinal tracts and motor neurons.	UMN and LMN symptoms.	Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) M > F, most common motor neuron disease, mutation in copper-zinc oxide dismutase, chromosome 21.
Sensory pathway lesions	Dorsal column	Destruction of the dorsal column.	Loss of tactile discrimination and position and vibration sensation; shooting pain and paresthesias; **Romberg's sign.**	Tabes dorsalis in **syphilis** (Charcot joints, loss of deep tendon reflexes).
Combined motor and sensory lesions	*Spinal cord* hemisection (Brown-Séquard syndrome)	*Damage to:* ▪ Dorsal columns. ▪ Lateral corticospinal tract. ▪ Lateral spinothalamic tract. ▪ Ventral (anterior) horn.	*Gives rise to:* ▪ Ipsilateral loss of tactile discrimination, position, vibration. ▪ Ipsilateral spastic paresis. ▪ Contralateral loss of pain and temperature sensation. ▪ Ipsilateral Horner's. ▪ Ipsilateral flaccid paralysis.	*Trauma.*
	Ventral/anterior spinal artery occlusion/ ischemia	Infarction of anterior two-thirds of spinal cord; damage is similar to hemisection but sparing dorsal columns and Lissauer's tract; however, **bilateral** damage to corticospinal tracts to sacral parasympathetic centers at S2–S4.	Similar to hemisection but no loss of tactile discrimination, position, vibration sense; however, results in urinary and stool incontinence; if **T1 or above**, bilateral Horner's syndrome.	Embolus, aortic dissection.
	Subacute combined degeneration	Damage to: ▪ Dorsal columns. ▪ Lateral corticospinal tract. ▪ Spinocerebellar tractss.	Results in: ▪ Bilateral loss of tactile discrimination, position, vibration sense. ▪ Bilateral spastic paresis. ▪ Bilateral upper and lower ataxia.	Vitamin B_{12} deficiency, pernicious anemia, **Friederich's ataxia** (autosomal recessive, no treatment, 40-year life-span).

(continues)

TABLE 6-19. Lesions of the Spinal Cord *(continued)*

Category	Lesion	Mechanism	Clinical Manifestation	Examples/Other Facts
Combined motor and sensory lesions (continued)	Syringomyelia	Central cavitation of the **cervical** cord (C8–T1) of unknown etiology; damage to: ▪ Ventral white commissure. ▪ Ventral horns.	Results in: ▪ Bilateral loss of pain and temperature sensation. ▪ Bilateral flaccid paralysis of intrinsic muscles of the hands.	Commonly seen with Arnold-Chiari syndrome; referred to as the sensation of wearing a "cape over the shoulders."
	Multiple sclerosis	Random, asymmetric autoimmune mediated demyelination of axons of cervical segments of the spinal cord as well as in the brain; pathology shows **oligodendrocyte loss** and **reactive gliosis.**	**Charcot's triad**: ▪ Scanning speech. ▪ Nystagmus. ▪ Intention tremor. Also spastic paresis, sensory loss, **MLF syndrome.**	Most commonly found in females 30–40 years old in temperate zones; Marburg variant (fulminant with death before age 10; Devic's syndrome: optic neuritis; IgG oligoclonal bands found in CSF; treated with steroids, interferon beta.
PNS lesions	Guillain–Barré syndrome	Demyelination and edema of motor fibers of ventral roots and peripheral nerves; commonly involves upper cervical roots and cranial nerves.	Facial diplegia, papilledema from elevated protein levels, paresthesias, fatal **respiratory paralysis.**	**Albuminocytologic dissociation:** Elevated protein in the CSF **without** pleocytosis.
Intervertebral disk herniation	90% L4–S1 10% C5–C7	Prolapse, herniation of the **nucleus pulposus** through defective annulus fibrosus and into vertebral canal, impinging on spinal roots.	Results in paresthesias, pain, sensory loss, hyporeflexia, muscle weakness.	Must screen for this in the setting of back or neck pain.
Terminal cord syndromes	Cauda equina syndrome	Impingement of roots L3Co1 from a nerve root tumor, ependymoma, dermoid tumor, lipoma.	Results in: ▪ Radicular **unilateral** pain. ▪ Loss of sensation in **unilateral** saddle-shaped area. ▪ Unilateral muscle atrophy and absent patellar (L3) and ankle (S1) jerks. ▪ **Mild** incontinence and sexual dysfunction. ▪ **Gradual** and **unilateral** onset.	Surgical emergency!

TABLE 6-19. Lesions of the Spinal Cord *(continued)*

Category	Lesion	Mechanism	Clinical Manifestation	Examples/Other Facts
Terminal cord syndromes (continued)	Conus medullaris syndrome	Impingement of S3–Co from intramedullary tumor (ependymoma).	Results in: ▪ **Bilateral** mild pain. ▪ Loss of sensation in **bilateral** saddle-shaped area. ▪ **Mild** muscle weakness, **preserved** reflexes. ▪ **Severe** incontinence and sexual dysfunction. ▪ **Sudden** and **bilateral** onset.	

Cranial Nerve Lesions

Although most lesions are straightforward, there are some frequently tested peculiarities (see Table 6-22):

- Facial lesions are divided into upper motor neuron lesions (UMN) and lower motor neuron lesions (LMN).
- UMN lesion:
  - Lesion in the motor cortex or connection between the cortex and the facial nucleus.
  - Leads to paralysis of the **contralateral lower face only.**
- LMN lesion (**Bell's palsy**; see Figure 6-47):
  - Lesion of the facial nucleus or facial nerve.
  - Leads to paralysis of the ipsilateral **upper and lower face.**

MNEMONIC

Bell's palsy is seen in **AL**exander **Bell** with **STD:**
AIDS
Lyme disease
Sarcoid
Tumors
Diabetes

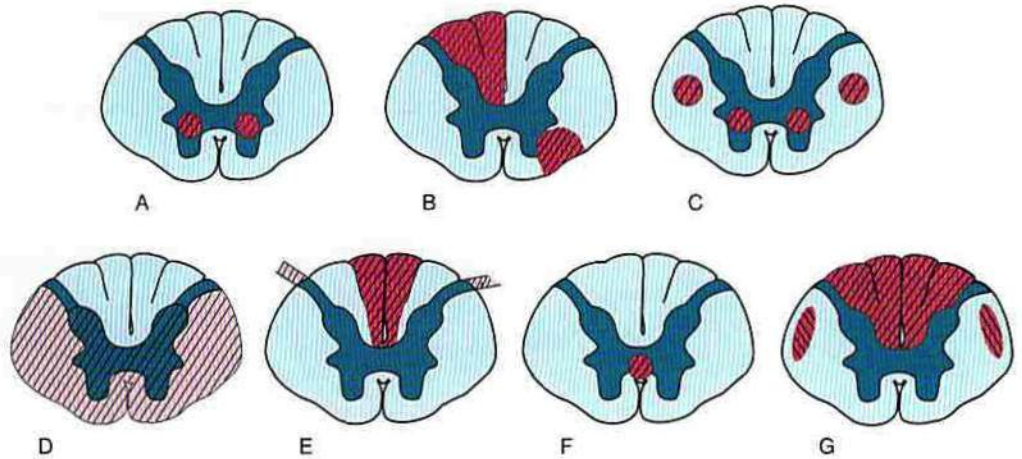


FIGURE 6-43. Patterns of spinal cord lesions. Shaded areas demarcate areas commonly lesioned in specific diseases. (A) Poliomyelitis and Werdnig-Hoffmann disease: Lower motor neuron lesions only due to destruction of anterior horns; flaccid paralysis. (B) Multiple sclerosis: Mostly white matter of cervical region; random and asymmetric lesions, due to demyelination; scanning speech, intention tremor, nystagmus. (C) ALS: Combined upper and lower motor neuron deficits with no sensory deficit; both upper and lower motor neuron signs. (D) Complete occlusion of ventral artery; spares dorsal columns and tract of Lissauer. (E) Tabes dorsalis (ternary syphilis): Degeneration of dorsal roots and dorsal columns; impaired proprioception, locomotor ataxia. (F) Syringomyelia: Crossing fibers of corticospinal tract damaged; bilateral loss of pain and temperature sensation. (G) Vitamin B_{12} neuropathy and Friedreich's ataxia: Demyelination of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts; ataxic gait, hyperreflexia, impaired position and vibration sense.

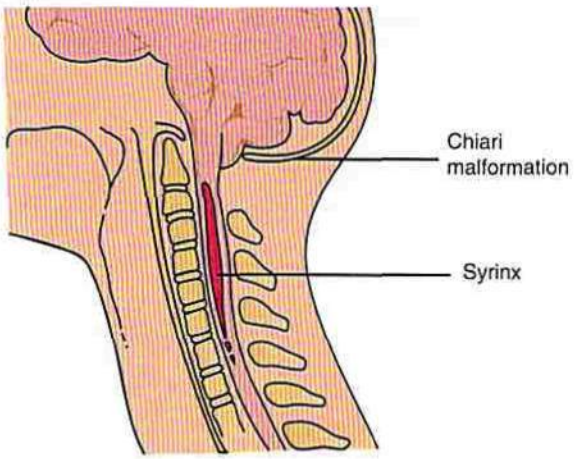


FIGURE 6-44. Syringomyelia in sagittal section. Involves enlargement of the central canal of the spinal cord, damaging fibers of the spinothalamic tract. Sensory loss is often described as feeling like one is wearing a cape over one's shoulders because it is most commonly found in C8–T1. Often seen in Arnold-Chiari malformation.

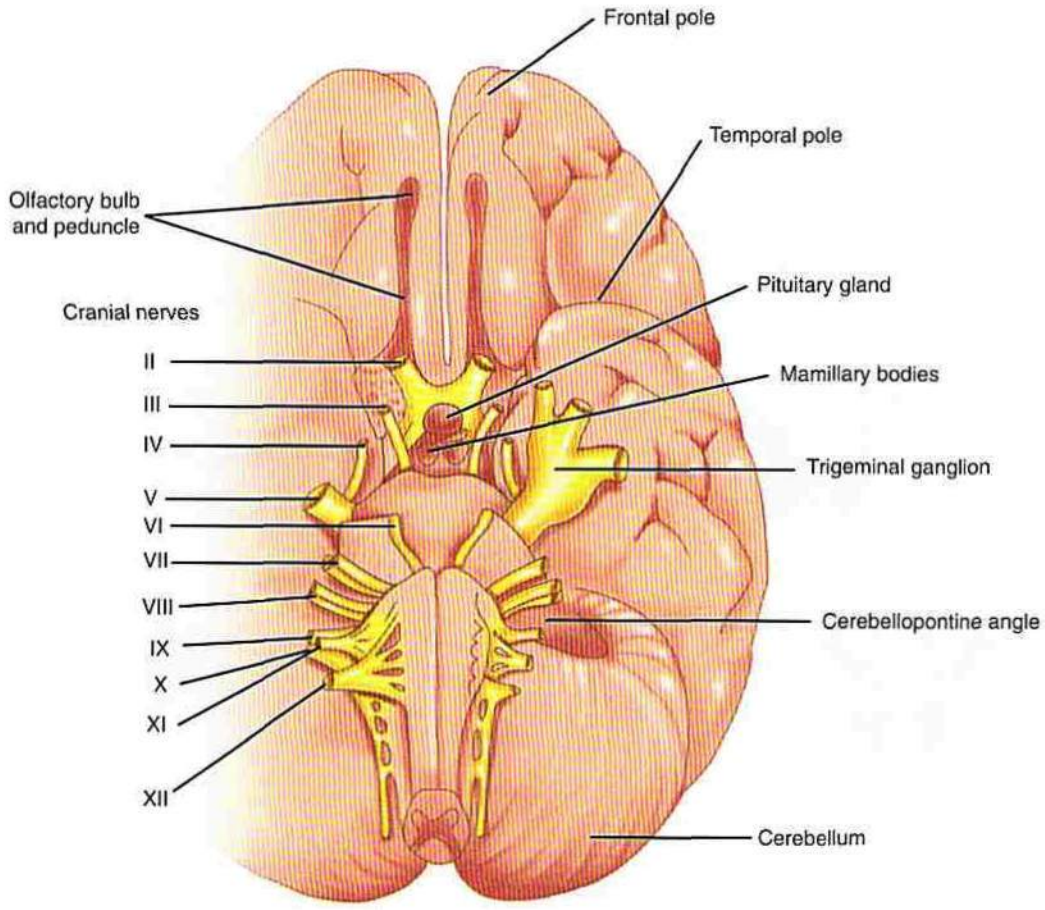


FIGURE 6-45. Anatomic exits of cranial nerves. The cranial nerves that are factors of 12 (II, III, IV, VI, and XII) exit near the midline while the rest exit laterally. Of these that exit near the midline, III and IV exit at the level of the midbrain, VI at the level of the pons, and XII at the level of the medulla.

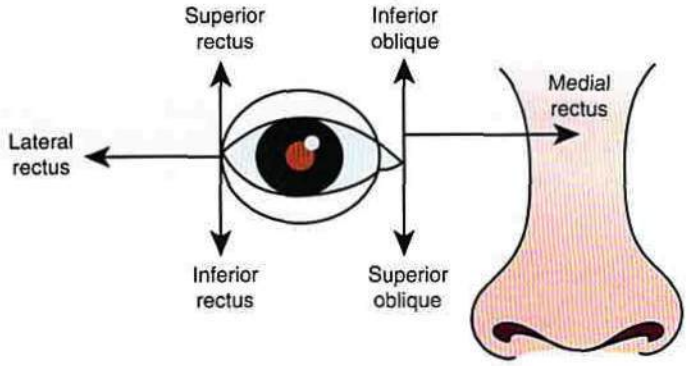


FIGURE 6-46. Extraocular muscles and their corresponding eye motions. (Modified, with permission, from Aminoff MJ, Greenberg DA, Simon RP. *Clinical Neurology*, 6th ed, New York: McGraw-Hill, 2005: Figure 4-5C.)

SENSORY PATHWAYS

Visual System

The visual system performs several important functions, including vision, pupillary reflex, near and far accommodation, and coordination of eye movements or gaze.

VISUAL PATHWAY (SEE FIGURE 6-48)

- **Photoreceptors** of the retina: Include **rods** that mediate black and white vision and **cones** that mediate color vision.
- **Ganglion cells** of the retina: Receive input from the rods and cones via other intermediary cells and send information down axons that form the

TABLE 6-20. Cranial Nerves

Cranial nerves

Nerve	CN	Function	Type	Mnemonic
Olfactory	I	Smell.	Sensory	Some
Optic	II	Sight.	Sensory	Say
Oculomotor	III	Eye movement, pupil constriction, accommodation, eyelid opening.	Motor	Marry
Trochlear	IV	Eye movement.	Motor	Money
Trigeminal	V	Mastication, facial sensation.	Both	But
Abducens	VI	Eye movement.	Motor	My
Facial	VII	Facial movement, taste from anterior 2/3 of tongue, lacrimation, salivation (submaxillary and sublingual glands), eyelid closing.	Both	Brother
Vestibulocochlear	VIII	Hearing, balance.	Sensory	Says
Glossopharyngeal	IX	Taste from posterior 1/3 of tongue, swallowing, salivation (parotid gland), monitoring carotid body and sinus chemo- and baroreceptors.	Both	Big
Vagus	X	Taste from epiglottic region, swallowing, palate elevation, talking, thoracoabdominal viscera, monitoring aortic arch chemo- and baroreceptors.	Both	Brains
Accessory	XI	Head turning, shoulder shrugging.	Motor	Matter
Hypoglossal	XII	Tongue movement.	Motor	Most

TABLE 6-21. Cranial Nerve Exits

Cranial nerve and vessel pathways	Cribriform plate (CN I). Middle cranial fossa (CN II–VI)—through sphenoid bone: 1. Optic canal (CN II, ophthalmic artery, central retinal vein) 2. Superior orbital fissure (CN III, IV, V_1, VI, ophthalmic vein) 3. Foramen Rotundum (CN V_2) 4. Foramen Ovale (CN V_3) 5. Foramen spinosum (middle meningeal artery) Posterior cranial fossa (CN VII–XII)—through temporal or occipital bone: 1. Internal auditory meatus (CN VII, VIII) 2. Jugular foramen (CN IX, X, XI, jugular vein) 3. Hypoglossal canal (CN XII) 4. Foramen magnum (spinal roots of CN XI, brain stem, vertebral arteries)	Divisions of CN V exit owing to Standing Room Only.

optic nerve (CN II). Ganglion cells from the **nasal** hemiretina project to the **contralateral** lateral geniculate nucleus (LGN), and those from the **temporal** hemiretina project to the **ipsilateral** LGN. Thus, vision from the right visual field is projected to the left LGN and vice versa.

- The **optic nerve** projects from the optic cup at the posterior aspect of the eye through the optic canal to the optic chiasm, where the fibers split.
  - Lesions of the optic nerve or the retina result in ipsilateral blindness with loss of the direct pupillary light reflex (light in the ipsilateral eye produces no papillary constriction).
  - **Junction scotoma:** Lesions of the optic nerve at the optic chiasm result in disruption of fibers that originate in the contralateral inferior nasal quadrant and loop into the optic nerve. This results in ipsilateral blindness plus a contralateral upper temporal quadrant defect known as a **junction scotoma.**

TABLE 6-22. Frequently Tested Cranial Nerve Lesions

Cranial Nerve	Note on Lesion
III	Triad of ptosis, blown pupil, and "down and out" eyes.
VII	**Bell's palsy**, paralysis of **both** the upper and lower face.
X	Uvula deviates **away** from the side of lesion.
XI	Weakness turning head to **contralateral** side of lesion.
XII	Tongue deviates **toward** the side of lesion ("lick your wounds").

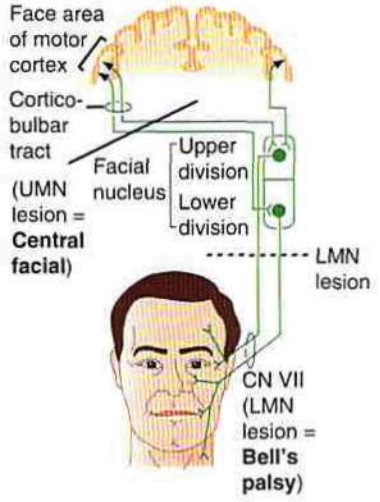


FIGURE 6-47. Facial lesions. Notice how the upper face receives input from the cortex on both sides, thus a unilateral UMN lesion will spare the upper face due to sparing of the contralateral fibers that are innervating the ipsilateral facial nucleus. However, a unilateral LMN lesion will disrupt all fibers from the facial nucleus, producing paralysis of the entire face.

- **Papilledema:** Results from congestion of the optic disk and pressure on the root of the optic nerve from increased ICP. Results in **enlarged blind spots** with **preserved visual acuity.** Commonly due to mass-occupying lesions in the brain or severe hypertension.
- **Optic chiasm:** Fibers from the two nasal hemiretinas decussate, and those from the temporal hemiretinas continue without decussation.
  - A **midsagittal lesion** produces **bitemporal hemianopsia**, usually from an enlarging pituitary tumor.

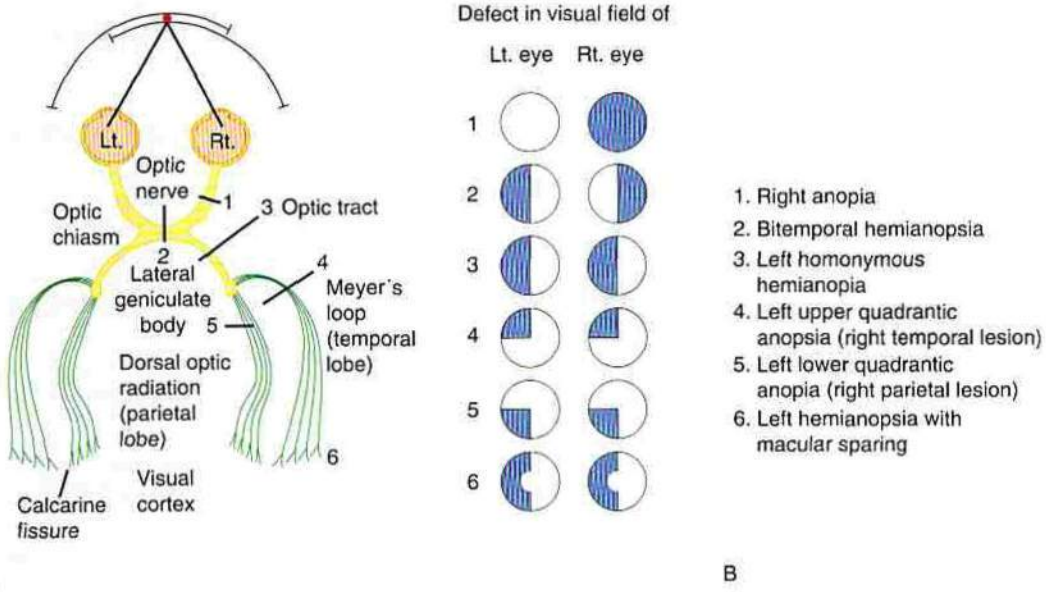


FIGURE 6-48. Visual pathways and associated lesions with clinical manifestations. (A) Visual pathway leading from retina to visual cortex. (B) Lesions along the pathway and corresponding clinical manifestations. Note that lesions proximal to the chiasm can be associated with monocular and ipsilateral defects, and lesions distal to the chiasm lead to contralateral and binocular defects.

KEY FACT

Lesions of the **afferent pathway** or CN II result in loss of the direct pupillary reflex with preservation of the indirect papillary reflex **(Marcus Gunn pupil).**

Lesions of the **efferent pathway** or CN III result in complete paralysis of the ipsilateral pupil.

KEY FACT

Argyll Robertson pupil (pupillary light-near dissociation) is the lack of pupillary constriction in response to light, with preservation of pupillary constriction in response to near stimulus. It is often referred to as **"prostitute's pupil"** because it "accommodates, but doesn't react." Seen in **syphilis** and **diabetes.**

KEY FACT

Adie's pupil is a large pupil similar to the **Argyll Robertson pupil**; it retains some reaction to light, but reacts very slowly. Seen in women with diminished knee and ankle reflexes.

- A **lateral lesion** produces **contralateral nasal hemianopia,** usually from a calcified internal carotid artery.
- **Bilateral lateral lesions** produce **binasal hemianopia**, usually from a calcified internal **carotid** artery.

- **Optic tract:** Formed from fibers from the ipsilateral temporal hemiretina and contralateral nasal hemiretina. These nerve fibres travel from the optic chiasm to the ipsilateral **LGN, pretectal nuclei,** and **superior colliculus.**
- **LGN:** Site where optic tract fibers terminate and synapse. Fibers from the LGN then project to the primary visual cortex (Brodmann's area 17) through the **geniculocalcarine tract** or **visual radiation.**
  - A **lesion** of the optic tract or LGN produces **contralateral hemianopia.**
- **Geniculocalcarine tract (visual radiation)** projects through two divisions: the **upper division** and the **lower division (Meyer's loop).**
  - A lesion of the **upper division** results in contralateral lower quadrantanopia. If bilateral, it is called **lower altitudinopia.**
  - A lesion of **Meyer's loop** results in contralateral upper quadrantanopia or **"pie in the sky."** If bilateral, it is called **upper altitudinopia.**
- **Visual cortex:** The posterior area receives **macular input** or central vision, the intermediate area receives **perimacular input** or peripheral vision, and the anterior area receives **monocular input.**
  - Lesions result in loss of central, peripheral, or monocular vision, depending on their location.

The **pupillary light reflex pathway** is mediated by the parasympathetic nervous system. It relies on an afferent pathway through CN II and an efferent pathway through CN III (see Figure 6-49).

Retinal ganglion cells → CN II (afferent pathway) → **pretectal nucleus** of the midbrain → **Edinger-Westphal nucleus** of CN III (preganglionic parasympathetic fibers) → CN III (efferent pathway) → **ciliary ganglion** (postganglionic parasympathetic fibers) → sphincter muscle of the **iris.**

The **pupillary dilation pathway** is mediated by the sympathetic nervous system. Lesions → ipsilateral **Horner's syndrome.**

The **near reflex and accommodation pathway** allows pupils to constrict and focus on near and far objects.

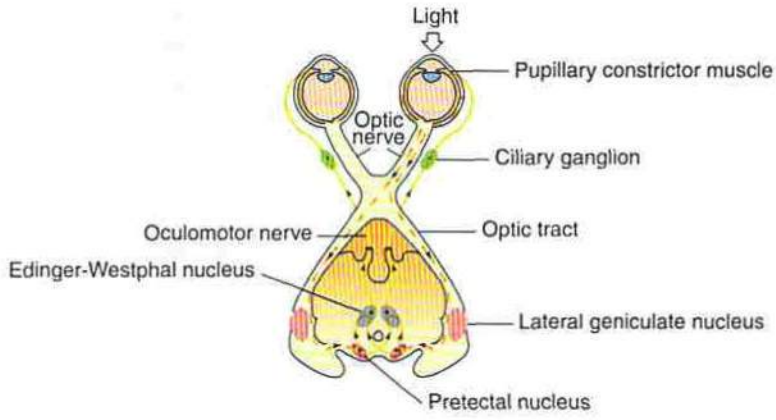


FIGURE 6-49. Pupillary light reflex pathway.

Auditory System

The auditory system can detect frequencies of 20–20,000 Hz. The afferent of the auditory system is CN VIII, the cochlear nerve.

Auditory Pathway (See Figure 6-50):

Hair cells of the **organ of Corti** transmit to the

- bipolar cells of the **spiral ganglion**, that in turn stimulate the
- cochlear nerve (enters the brain stem at the **cerebellopontine angle**) ascends to the cochlear nuclei, which sends off fibers that
- decussate via the **trapezoid body**, and travel to the
- contralateral **superior olivary nucleus**
- ascends via the **lateral lemniscus** to the
- **nucleus of the inferior colliculus**
- **medial geniculate nucleus (MGN)**
- transverse temporal **gyri of Heschl**/primary auditory cortex (Brodmann's areas 41 and 42).

Hearing Defects

- **Conduction deafness:** Caused by blockage that prevents sound waves from reaching the organ of Corti. The defect is in the **external** or **middle** ear. May be due to **obstruction** (i.e., wax), **otosclerosis**, or **otitis media.**
- **Nerve deafness:** Caused by disease of the cochlea, cochlear nerve, or central auditory pathways. Usually due to degeneration of the organ of Corti. May also be due to tumors that disrupt the cochlear nerve (e.g., **acoustic neuroma**).

KEY FACT

Strachan's syndrome results from vitamin B_1 intoxication. It produces the following set of symptoms:

- **Nerve** deafness
- Optic atrophy
- Spinal ataxia

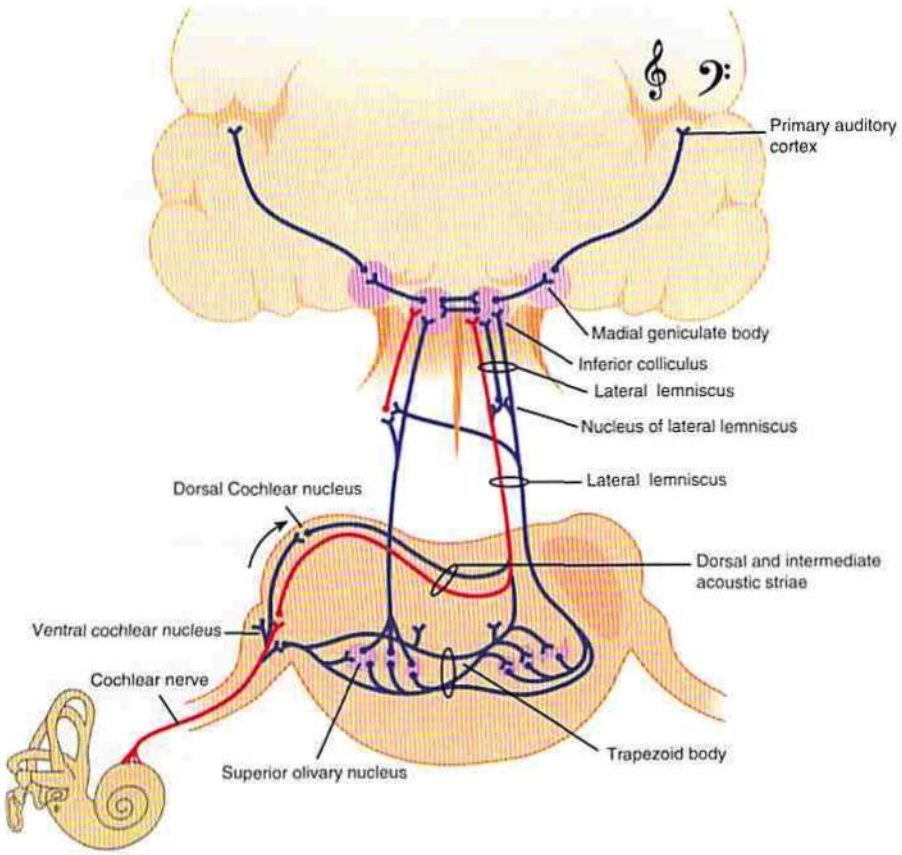


FIGURE 6-50. Auditory pathway. (Modified, with permission, from Noback CR. *The Human Nervous System*, 3rd ed, New York: McGraw-Hill, 1981.)

KEY FACT

Brain stem auditory evoked potential (BAEP) testing is another way to test hearing, especially in infants who are unable to communicate whether they hear a sound. Sounds are presented to each ear separately. Electrodes on the scalp record the responses of the brain.

- There are two major tests of hearing that can be done at the bedside to differentiate between conduction and nerve deafness:
  - **Weber's test:** Place a vibrating tuning fork on the top of the skull. Ask the patient which side sounds louder.
    - In **conduction deafness,** the sound is louder on the **affected** side.
    - In **nerve deafness,** the sound is louder on the **unaffected** side.
  - **Rinne's test:** Place a vibrating tuning fork on the mastoid process behind the ear until the patient can no longer hear the sound. The patient is using **bone conduction** during this phase of the test. Once the patient no longer hears the sound, the tuning fork is held in front of the ear. Normally, the patient still hears the sound using **air conduction.** Normally, air conduction > bone conduction.
    - In **conduction deafness,** bone conduction is greater than air conduction and Rinne's test is abnormal.
    - In **nerve deafness,** air conduction is greater than bone conduction and Rinne's test is normal.

Vestibular System

The vestibular system maintains balance and coordinates head and eye movements. Vertigo results from disruption of the vestibular system.

Labyrinth

- **Kinetic labyrinth:** Consists of three semicircular canals (superior, lateral, and posterior) that are filled with a fluid called **endolymph.** Provides information on **angular acceleration and deceleration** of the head. **Hair cells** lie in the **ampulla** and are activated by endolymph flow.
- **Static labyrinth:** Consists of the **utricle** and **saccule** and responds to **linear acceleration** of the head, including **gravity. Hair cells** reside on the otolithic membrane, and bending toward the longest cilium **(kinocilium)** results in activation.

KEY FACT

Foster Kennedy syndrome occurs when a meningioma of the olfactory groove compresses the olfactory and optic nerves. Produces the following set of symptoms:

- Ipsilateral anosmia (inability to detect smells)
- Ipsilateral optic atrophy
- Contralateral papilledema

Vestibular Pathways

Hair cells of labyrinth structures → **vestibular ganglion** → **vestibular nuclei** → **cerebellum, MLF, spinal cord, thalamus.**

Olfactory System

The olfactory system mediates the sense of smell and involves CN I, the olfactory nerve. It is the only sensory modality that is not relayed by the thalamus before reaching the cortex. Thus, it is thought to be one of the most primal sensory systems.

KEY FACT

Kallman's syndrome results from lack of proper formation of the olfactory tract. Hypothalamic neurons rely on the olfactory tract to migrate to their destinations. Produces the following set of symptoms:

- Anosmia
- Hypogonadism
- Infertility

Olfactory Pathway

Olfactory receptor cells → **mitral cells of the olfactory bulb** → **olfactory tract/nerve** → **primary olfactory cortex** and **amygdala.**

Gustatory System

The gustatory system mediates taste and is carried by two major nerves: the special sensory division of CN VII (facial nerve), which supplies the anterior two-thirds of the tongue, and CN IX (glossopharyngeal nerve), which supplies the posterior one-third of the tongue.

Gustatory Pathway

- Taste buds of the anterior two-thirds of the tongue → intermediate nerve, chorda tympani, lingual nerve (branch of CN V3) → geniculate gan-

glion (cell bodies of the taste buds) → solitary tract and nucleus → ventral posteromedial nucleus of the thalamus → gustatory cortex (parietal operculum).

- Taste buds of the posterior one-third of the tongue → glossopharyngeal nerve (CN IX) → petrosal (inferior) ganglion → solitary tract and nucleus → ventral posteromedial nucleus of the thalamus → gustatory cortex (parietal operculum).

Histology

CELLS OF THE NERVOUS SYSTEM

Neurons

The basic subunits of the CNS and PNS. There are several variants (sensory, motor, and interneuron) that all share similar basic structures (see Figure 6-51).

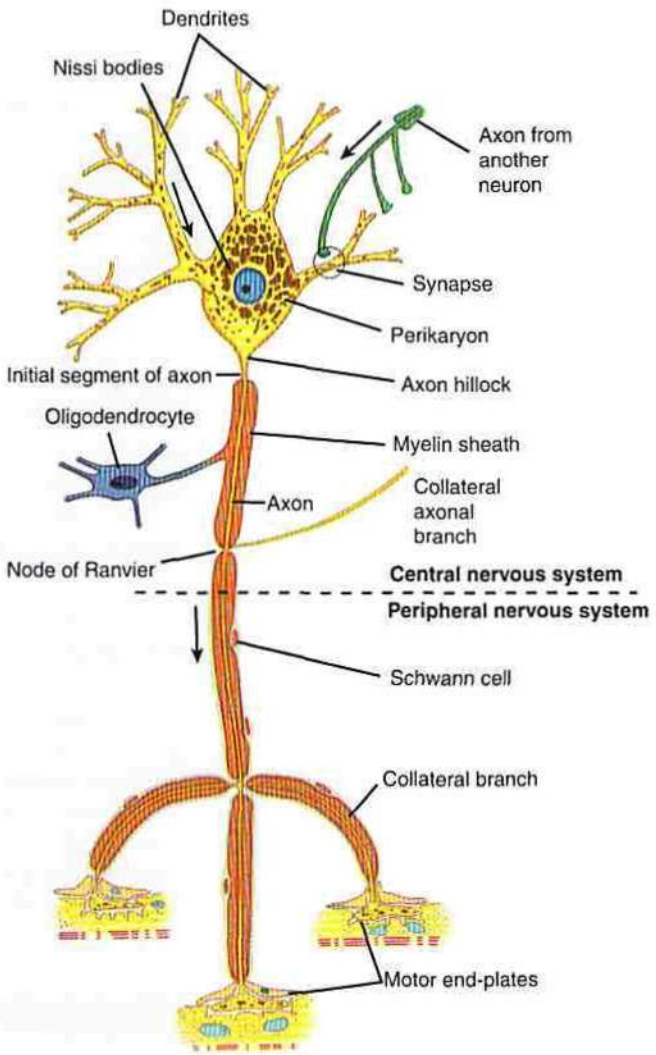


FIGURE 6-51. Central and peripheral neurons. Basic structure of neurons. Note that in the PNS, axons are myelinated by Schwann cells, whereas in the CNS the axons are myelinated by oligodendrocytes. (Modified, with permission, from Waxman SG. *Clinical Neuroanatomy*, 25th ed, New York: McGraw-Hill, 2003.)

KEY FACT

Proteins and substances are transported anterograde (away from the cell body) or retrograde (toward the cell body) along microtubules via **kinesins** and **dyneins,** respectively.

KEY FACT

Myelination of neurons in the CNS occurs by oligodendrocytes. Each oligodendrocyte myelinates multiple axons. Myelination in the periphery occurs by Schwann cells, where each Schwann cell myelinates only one axon.

KEY FACT

Anesthetics such as lidocaine work by blocking sodium channels in the axon and blocking the conduction of APs triggered by painful stimuli.

KEY FACT

Wallerian degeneration occurs in a segment of axon after it has been disconnected from the cell body. In the periphery, degradation and phagocytosis of the axon and myelin is followed by proliferation of Schwann cells. **Chromatolysis** occurs in a cell body when an axon has been cut off.

KEY FACT

HIV-infected microglia form multinucleated giant cells.

Neurons contain the following basic components:

- Cell body (**soma**): Contains the nucleus, organelles, and prominent clusters of rough endoplasmic reticulum, the latter visualized as **Nissl substance.**
- Dendrites: Afferent single or multiple extensions of the cell membrane that transmit or receive signals from other neurons or the environment to the neuron. They also contain Nissl substance.
- Axons: Efferent extensions of the cell membrane that send signals **away** from the cell body to other neurons or to end organs. They may be myelinated or unmyelinated,

Neurons may have any number of dendrites and axons, which can be used for classification purposes:

- **Unipolar** neurons have one dendrite or one axon.
- **Pseudo-unipolar** neurons have one process that branches into a dendrite and an axon.
- **Bipolar** neurons have one dendrite and one axon.
- **Multipolar** neurons have many dendrites and axons.

Neuronal axons contain both areas that are myelinated and those that are unmyelinated,

- **Myelin:** Multiple layers of phospholipid that form a sheath around an axon. It contains ion channels that open to allow current to flow across the axon membrane. Myelination also permits fast transmission of APs along the axon.
- **Nodes of Ranvier:** Areas of naked axon in between areas encased by myelin. Allows rapid salutatory conduction of action potentials (APs) along the axon.

Neuroglia

Neurons are maintained by supportive cells known as neuroglia. Neuroglia come in several forms:

- Astrocytes: Cells that repair and provide nutritional support to neurons, maintain the BBB, and regulate the composition of CSF. They contain glial fibrillary acidic protein (**GFAP**); stains for GFAP are used to assist in the differential diagnosis of neurologic lesions.
- Ependymal cells: A single layer of cells lining the ventricles.
- Microglia: Phagocytes of mesodermal origin with irregular nuclei and little cytoplasm. They proliferate around injured nerve tissue and transform into large ameboid phagocytic cells in response to tissue damage.
- Oligodendroglia: Each cell may myelinate up to 30 neurons in the CNS. Destroyed in demyelinating diseases such as **multiple sclerosis.**
- Schwann cells: Each cell myelinates one PNS axon. Gaps between Schwann cells constitute the nodes of Ranvier. They assist in axonal regeneration by creating a pathway for axon growth and secreting growth factors. With mutation of tumor suppressor NF2, may give rise to **schwannomas,** located in the internal acoustic meatus (**acoustic neuroma**).

INTERCELLULAR COMMUNICATION

Synapses

Neurons communicate with each other through **synapses.** Synapses involve the following structures (see Figure 6-52):

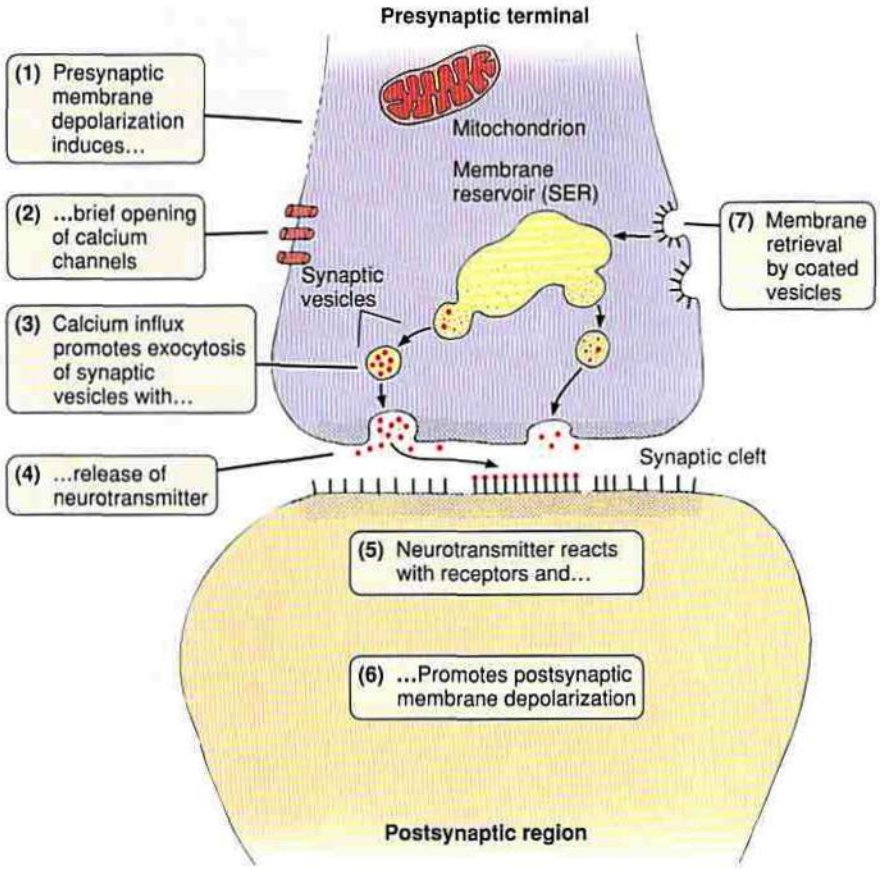


FIGURE 6-52. Steps of synaptic transmission. The small spikes on the postsynaptic membrane represent receptors for neurotransmitters. SER = **Smooth endoplasmic reticulum**. (Reproduced, with permission, from Junqueira LC, Carneiro J. *Basic Histology, 11th ed*, New York: McGraw-Hill, 2005: 158.)

- Presynaptic membrane: Contains voltage-gated calcium channels that open in response to APs.
- Secretory vesicles: Contain the neurotransmitter and rest in the cytoplasm, until calcium influx recruits them to the presynaptic axon terminal for exocytosis.
- Synaptic cleft: Site where exocytosed neurotransmitter molecules diffuse across to the postsynaptic membrane.
- Postsynaptic membrane: Contains receptors for various neurotransmitters coupled to sodium channels.
- Receptors: Bind the neurotransmitter and facilitate depolarization of the postsynaptic membrane by activating sodium channels.
- Ion channels: Include sodium, potassium, and calcium channels. Sodium channels are responsible for depolarization (AP); potassium channels are responsible for repolarization (termination of the AP); and calcium channels are responsible for permitting increased calcium concentration that allows for muscle contraction in the PNS.

Neuromuscular Junction

Neurons communicate with muscle fibers through the neuromuscular junction (NMJ), which resembles a synapse except that the postsynaptic membrane is the membrane of a muscle fiber, also known as an **endplate.** The

neurotransmitter is always acetylcholine (Ach). Below is the sequence of events that takes place during activation of the NMJ (see Figure 6-53):

- A wave of depolarization propagates down the axon toward the axon terminal, promoting exocytosis of Ach (similar to the process in the synapse, described above).
- Nicotinic Ach receptors lie on the postsynaptic membrane and permit sodium to enter when bound to Ach.
- Voltage-gated calcium channels on the postsynaptic membrane open and allow calcium to enter and activate muscle contraction.
- Calcium enters the muscle cells, binds troponin, and moves tropomyosin off myosin, allowing actin to bind to myosin and muscle contraction to occur.
- Meanwhile, acetylcholinesterase (AchE) degrades Ach that remains in the synaptic cleft.

Diseases of the Neuromuscular Junction

Myasthenia gravis is an autoimmune disease in which antibodies attack the nicotinic Ach receptors, decreasing their numbers.

- Ptosis and/or diplopia is often the presenting symptom.
- Characteristically associated with muscle fatigue and weakness that progresses throughout the day or with repeated exertion.
- If left untreated, can lead to respiratory failure.

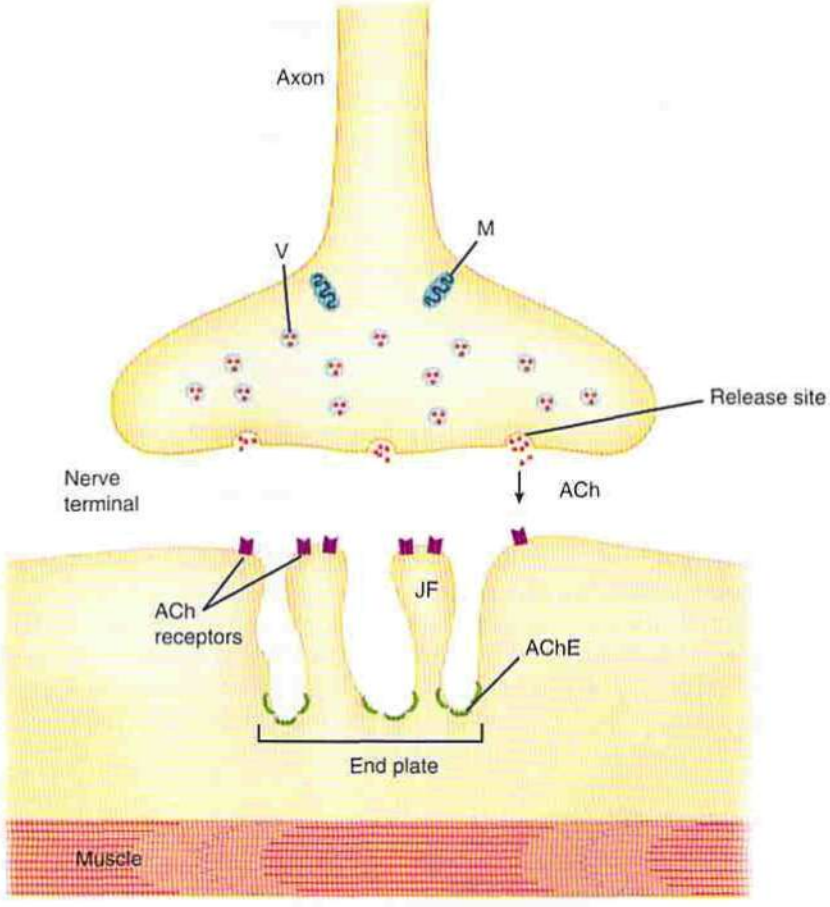


FIGURE 6-53. Neuromuscular junction. The "nerve terminal" is the pre-synaptic bouton. Ach = Acetylcholine; M = mitochondria; V = vesicles containing ach.

- Often associated with underlying thymoma.
- Diagnosis via the **tensilon test:** Administration of **edrophonium,** a short-acting AchE inhibitor, rapidly improves symptoms.

Lambert-Eaton syndrome is an autoimmune disease in which antibodies attack calcium channels in the muscle fibers.

- Weakness of large muscles (e.g., quadriceps) with initial exertion that improves with repeated use.
- Presents with difficulty rising from a chair.
- Associated with **small cell lung cancer.**

Sensory Corpuscles

Neurons receive sensory signals through the skin via specialized sensory organs: Meissner's, pacinian, Merkel's, and Ruffini's corpuscles, and Golgi tendon organs. Other sensory organs include joint receptors, stretch receptors, baroreceptors, and hair cells of the inner ear (see Table 6-23).

- Pacinian corpuscles: Mediate discrimination of coarse spatial differences.
- Meissner's and Merkel's corpuscles: Mediate discrimination of fine spatial differences.
- Joint capsule receptors: Sense flexion/extension of the joints.
- Muscle spindles: Sense muscle length.
- Golgi tendon organs: Sense tension of tendons and muscles.

Organization of Peripheral Nerves

Nerve fibers consist of axons and their myelin sheaths and are bundled together into peripheral nerve fibers. From outermost to innermost, the three layers of a nerve fiber are:

- **Epineurium** (dense connective tissue) surrounds the entire nerve.
- **Perineurium** (permeability barrier) surrounds a fascicle of fibers; must be rejoined in limb attachment surgery.
- **Endoneurium** surrounds a single nerve fiber (see Figure 6-54).

TABLE 6-23. Major Sensory Corpuscles

Sensory Corpuscle	Meissner's Corpuscle	Pacinian Corpuscle and Ruffini's Corpuscle	Merkel's Corpuscle	Golgi Tendon Organ	Spindle
Mediates:	Light touch	Pressure, vibration	Light crude touch	Contraction of tendons	Stretch
Description:	Small encapsulated	Large encapsulated	Tactile disks		
Location:	Dermis	Dermis	Dermis	Within tendon	Within muscle fiber
Location in the body:	Glabrous hairless skin, palms, and soles	Skin, joint capsules, ligaments, serous membranes, and mesenteries	Fingertips, hair follicles, and hard palate	Within tendon	Within muscle fiber

FLASH BACK

Development of the neural tube is complete by day 28 of pregnancy. This is important with respect to maternal folate levels because folate is necessary for DNA synthesis, which is essential for dividing cells.

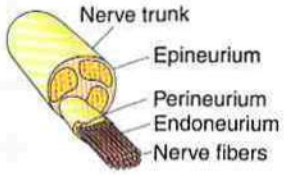


FIGURE 6-54. Layers of the nerve fiber.

KEY FACT

Carbamazepine and valproic acid have been strongly associated with the development of neural tube defects. Valproic acid is a folate antagonist.

KEY FACT

α-Fetoprotein is also elevated in hepatocellular carcinoma and yolk sac (endodermal sinus) tumors.

KEY FACT

The three markers tested in the triple screen test, done at 15–18 weeks of gestation, are hCG, estriol, and α-fetoprotein. High hCG and estriol coupled with low levels of α-fetoprotein indicate an increased risk of having a child with Down's syndrome.

Pathology

NEURAL TUBE DEFECTS

Congenital failure of the neural folds and coverings to fuse in the midline leads to deformities in the developing nervous system (see Figure 6-55). Clinical presentation varies in severity depending on which layer is defective (see Table 6-24). The development of these defects is associated with low maternal folic acid levels early in pregnancy. Therefore, babies of mothers taking folate supplements prior to conception have a decreased risk of neural tube defects. Elevated α-fetoprotein in amniotic fluid and maternal serum is diagnostic. In utero ultrasound can confirm the presence of a deformity.

VENTRICULAR SYSTEM MALFORMATIONS

Disruption in the flow of CSF in the subarachnoid space through the cerebral ventricles may lead to an increase in ICP (see Figure 6-56). Malformations may occur anywhere along the pathway and result in a decrease in CSF flow from either **direct blockage of the foramina** or **decreased resorption at the arachnoid granulations.** In either case, hydrocephalus results (representing an increase in ICP).

PRESENTATION

Hydrocephalus can often present with an enlarged calvarium if the cranial bones have not yet fused (i.e., the fontanelles are still present). Patients with increased ICP present with the cardinal signs of headache, vomiting without nausea, and papilledema.

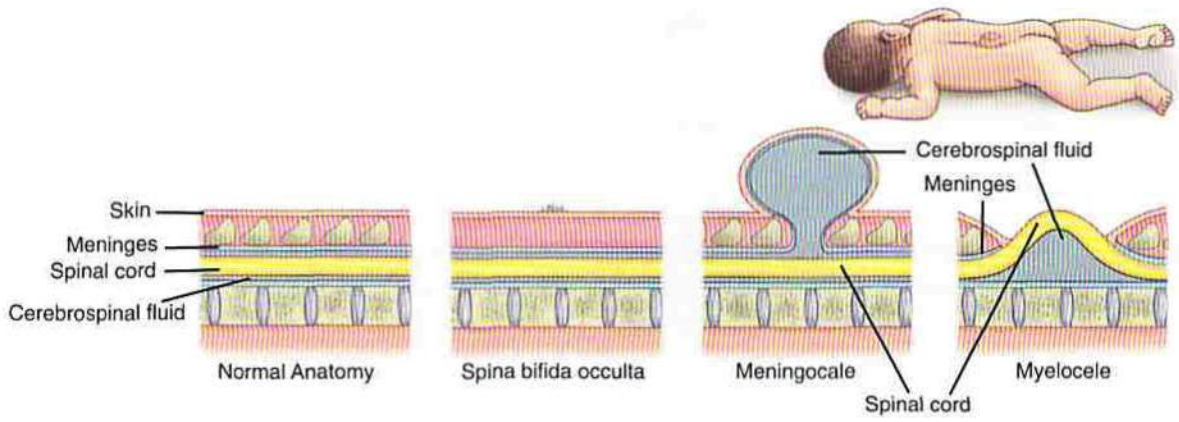


FIGURE 6-55. Schematic diagram of spinal column defects.

TABLE 6-24. Comparison of Neural Tube Defects

Type of Defect	Etiology	Presentation	Treatment/Prognosis
Spina bifida occulta	*Failure of the posterior vertebral arch* lamina to close around the spinal canal.	*May present with subcutaneous* lipoma or tuft of hair overlying the location of the defect.	*Most cases are asymptomatic* and generally found incidentally.
	Spinal cord and meninges remain inside the spinal canal.	No associated neurologic signs or symptoms.	
		Present in 10%–25% of the population.	
Meningocele	Failure of the neural canal to close, causing a herniation of the arachnoid and dura through the bony defect.	Cystic swelling usually in the lumbosacral region, with the lumbar cord only covered by meninges and skin.	Most cases are asymptomatic but must be distinguished from meningomyelocele.
	The spinal cord and nerve roots remain in the canal.	No associated neurologic signs or symptoms.	
Meningomyelocele	Defect 10 × more common than meningocele, characterized by herniation of spinal cord, roots, and meningeal covering through vertebral column defect.	Motor and sensory defects arising in the lower extremities from severe dysfunction of the nerves contained in the sac.	If only sacral cord affected, bladder and bowel sphincters are affected with sparing of the legs.
		Absent tendon reflexes.	If lumbar and sacral cord affected, the patient is paraplegic.
		Bowel and bladder dysfunction.	Complications include meningitis (because thin skin covering increases risk of infection), progressive hydrocephalus if associated with Arnold-Chiari malformation.
		Skin covering may rupture in utero or during birth.	Surgery to excise and close coverings may prevent fatal meningitis.
		Mental function intact if defect only affects lumbar region (i.e., no Arnold-Chiari malformation).	Ventricle shunt to diminish risk of progressive hydrocephalus.
Anencephaly	One of the most common and severe congenital malformations of the brain; results from failure of the anterior pore (rostral end) of the neural tube to close.	*Complete absence of brain* with rudimentary brain stem, cerebellum and spinal cord present.	*Close to 100% die within the first* postnatal week.
		Often associated with cardiac malformations.	

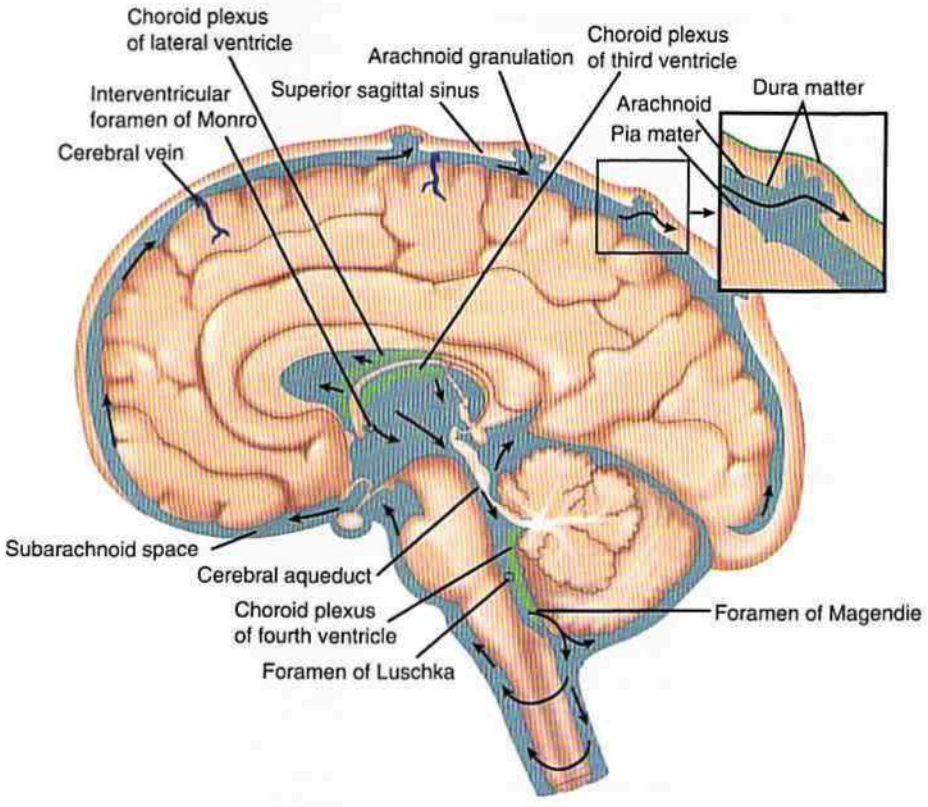


FIGURE 6-56. Diagram of cerebrospinal fluid flow through the ventricles.

KEY FACT

In patients suspected of having increased ICP, inspection for papilledema and loss of venous pulsations in the retina on physical exam as well as CT scan should be performed prior to lumbar puncture because of the danger of precipitating tonsillar herniation.

DIAGNOSIS

Made by imaging studies (ultrasound, CT, or MRI) showing abnormalities in CSF flow and ventricle dilation.

Malformations leading to hydrocephalus can be categorized according to whether they are communicating or noncommunicating.

- **Communicating:** No anatomic block of CSF flow between the ventricles and the subarachnoid space. Examples include meningitis and subarachnoid hemorrhage.
- **Noncommunicating:** Blockage of CSF flow from the ventricle to the subarachnoid space at any point in the ventricular system.

TREATMENT

Ventricular shunt.

NONCOMMUNICATING HYDROCEPHALUS

KEY FACT

Riboflavin inhibitors (isotretinoin), posterior fossa trauma, and viral infection (rubella, CMV) have been implicated in the development of Dandy-Walker malformation.

Blockage of CSF flow can lead to increased ICP, which causes dilation of the ventricles proximal to the blockage.

Dandy-Walker Malformation

Dilation of the fourth ventricle, often secondary to atresia of the foramina of Luschka and Magendie, results in **hypoplasia of the midline portion (vermis) of the cerebellum and enlargement of the posterior fossa** (see Figure 6-57).

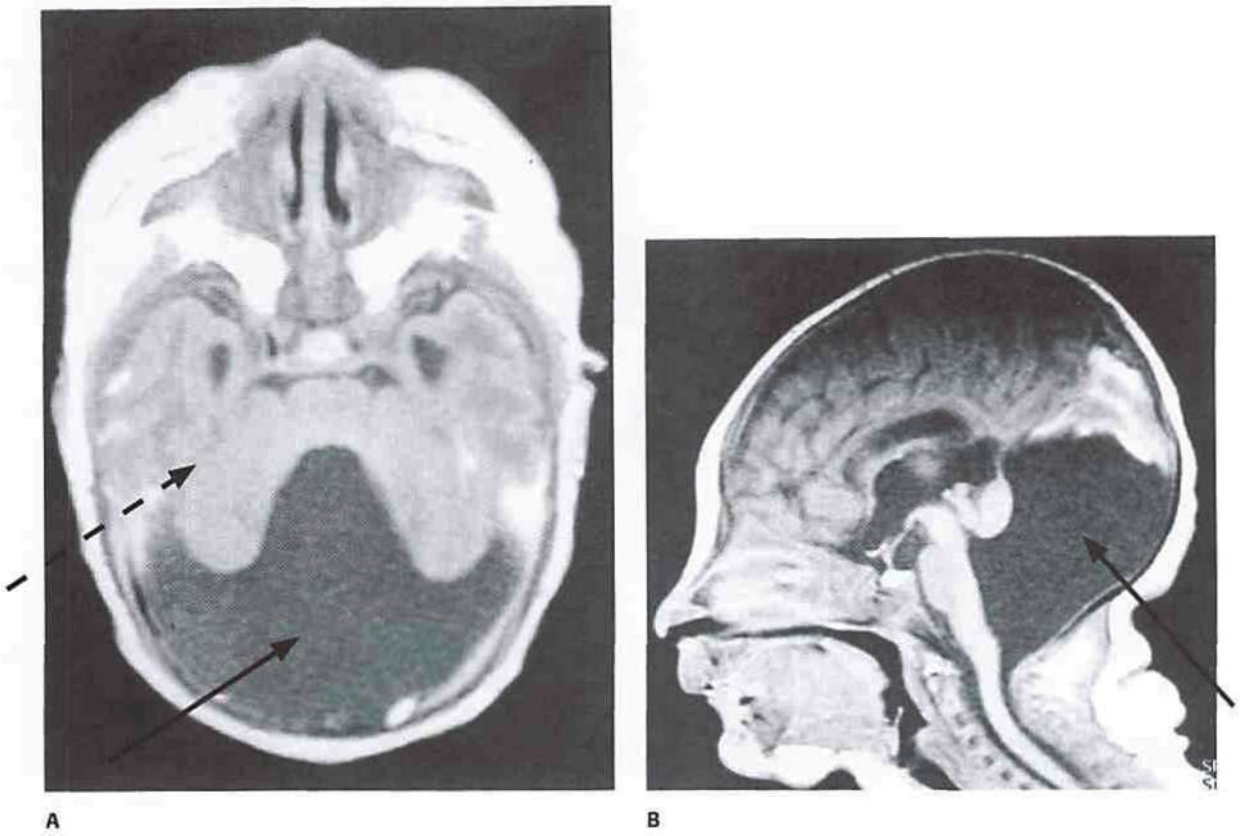


FIGURE 6-57. Dandy–Walker syndrome. MRI showing agenesis of the midline cerebellum and large midline cyst. Solid arrows indicate the dilated fourth ventricle, which occupies almost the entire posterior fossa. Dashed arrow indicates hypoplastic cerebellar vermis. (A) Axial view; (B) Sagittal view. (Reproduced, with permission, from Ropper AH, Brown RH. *Adams and Victor's Neurology*, 8th ed. New York: McGraw-Hill, 2005: 859.)

Presentation

Patients often present with developmental delay, enlarged head circumference, and signs and symptoms of hydrocephalus. Cerebellar involvement may result in difficulty with balance, spasticity, and poor fine motor control. The following are also observed:

- Cystic dilation of the fourth ventricle, causing the occipital bone to bulge posteriorly, displacing the tentorium upward.
- Aplastic cerebellar vermis.
- Deficient or absent corpus callosum.
- Dilation of the sylvian aqueduct and the third and lateral ventricles (proximal to the fourth ventricle and therefore affected by obstruction at the foramina of Magendie and Luschka).

Diagnosis

Ultrasound, MRI, or CT showing an enlarged posterior fossa with a midline cyst.

Treatment

Shunt to treat hydrocephalus and prevent herniation.

Prognosis

About 70%–90% of patients with this malformation develop obstructive hydrocephalus. Without treatment, they will have long-term neurologic deficits.

Congenital Aqueduct of Sylvius Stenosis

The most common cause of hydrocephalus in newborns leads to obstruction of CSF flow between the third and fourth ventricles. This results in dilation of the ventricles proximal to this obstruction, namely, the third and lateral ventricles.

Presentation

Dilation of the third and lateral ventricles along with clinical signs of papilledema, vomiting, and headache.

Diagnosis

MRI or CT showing enlarged third and lateral ventricles; the presence of hydrocephalus can be confirmed by clinical findings.

Treatment

Shunt, cerebral aqueductoplasty.

Prognosis

Simple aqueduct stenosis is associated with a very good outcome, with more than half of patients expected to complete normal schooling.

FLASH BACK

Arnold-Chiari malformation is associated with spina bifida, meningomyelocele type.

Arnold-Chiari Malformation

Caudal extension of the medulla and cerebellar vermis through the foramen magnum leads to noncommunicating hydrocephalus. This malformation is strongly associated with **syringomyelia** (segmental amyotrophy and sensory loss, with or without pain) and **meningomyelocele** (lumbar).

Presentation

Patients develop stridor and poor swallowing function secondary to brain stem dysfunction and bilateral vocal cord paralysis, platybasia (flattening of the base of the skull), and aqueductal narrowing. When associated with meningomyelocele, patients develop progressive hydrocephalus.

Diagnosis

The inferior portion of cerebellar tissue kinks the cervical cord, resulting in obstruction of the upward flow of dye, which yields a highly characteristic radiologic profile, particularly on sagittal MRI (see Figure 6-58).

Treatment

If unlikely to progress, no treatment is recommended, If disability is increasing, upper cervical laminectomy and enlargement of the foramen magnum is indicated,

Prognosis

Patients presenting with meningomyelocele or syringomyelia generally have a poor prognosis.

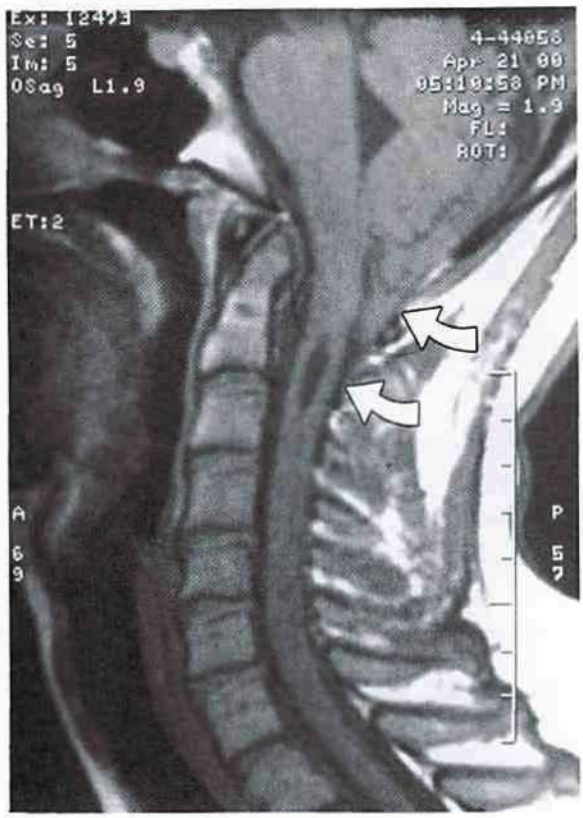


FIGURE 6-58. Chiari-Type malformation and developmental syringomyelia. T_1-Weighted MRI of the low-lying cerebellar tonsils below the foramen magnum and behind the upper cervical cord (upper arrow) and the syrinx cavity in the upper cord (lower arrow). (Reproduced, with permission, from Ropper AH, Brown RH. *Adams and Victor's Neurology*, 8th ed, New York: McGraw-Hill, 2005: 862.)

COMMUNICATING HYDROCEPHALUS

Normal CSF flow with abnormal absorption leads to dilation of all ventricles.

Hydrocephalus Ex Vacuo in the Elderly

Presentation

Ventricular dilation after significant neuronal loss (e.g., Alzheimer's disease, stroke) where CSF passively fills the vacant space. Results in symptoms of hydrocephalus with deficits in cognition.

Diagnosis

Imaging studies (MRI, CT) showing significant neuronal loss.

Treatment

Shunts are not helpful, as the underlying defect is loss of brain parenchyma.

Meningitis

Inflammation of the meningeal coverings in the CNS (brain and spinal cord) results from bacterial, viral, fungal, or parasitic infection. The consequent postmeningeal scarring and interstitial edema lead to decreased resorption of CSF at the arachnoid granulations and an increase in ICP. The elderly (> 60 years), the very young (< 3 years), and those living in close quarters (military barracks, dorms) are at increased risk.

Presentation

Meningismus (patient cannot touch chin to chest), nuchal rigidity, headache, and fever, as well as signs of elevated ICP.

Diagnosis

CT prior to lumbar puncture if focal neurologic deficits are present, CSF profile.

Treatment

Empiric antibiotic therapy.

Prognosis

Viral > 1% mortality rate; bacterial 25% mortality rate.

Subarachnoid Hemorrhage

Blood in the subarachnoid space (same space as the CSF) may derive from a ruptured berry aneurysm at the bifurcation of the anterior communicating artery or from congenital arteriovenous malformation. This results in communicating hydrocephalus because the blood clogs the arachnoid granulations, thereby preventing proper CSF resorption. Two percent of the U.S. population has aneurysms.

Presentation

Sudden-onset "worst headache of my life," bloody/xanthochromic spinal tap (yellow discoloration from degradation of RBCs), isolated CN III palsy, as well as decreased level of consciousness preceding signs of hydrocephalus.

Diagnosis

CT scan showing blood covering the surface of the brain (through the subarachnoid space) and angiogram to determine whether it is of spontaneous or traumatic etiology.

FLASH FORWARD

Berry aneurysms are associated with adult polycystic kidney disease, Ehlers-Danlos syndrome, and Marfan's syndrome. Additional risk factors include: old age, hypertension, smoking, and race (higher rates in African Americans).

Treatment

Surgical excision of the aneurysm or filling with metal coil (prior to rupture).

Prognosis

Forty-five percent die within 1 month following hospitalization.

Normal Pressure Hydrocephalus

In 50% of cases, an idiopathic intermittent increase in ICP occurs. Remaining causes include meningitis, subarachnoid hemorrhage, and atherosclerosis. Results from decreased resorption of CSF at the arachnoid granulations.

Presentation

Classic triad of bladder incontinence, dementia, and slowly developing ataxia with notably no papilledema or headaches.

Diagnosis

Clinical signs, with CT/MRI showing ventriculomegaly without proportional sulcal atrophy (parenchymal loss) or increased CSF (see Figure 6-59).

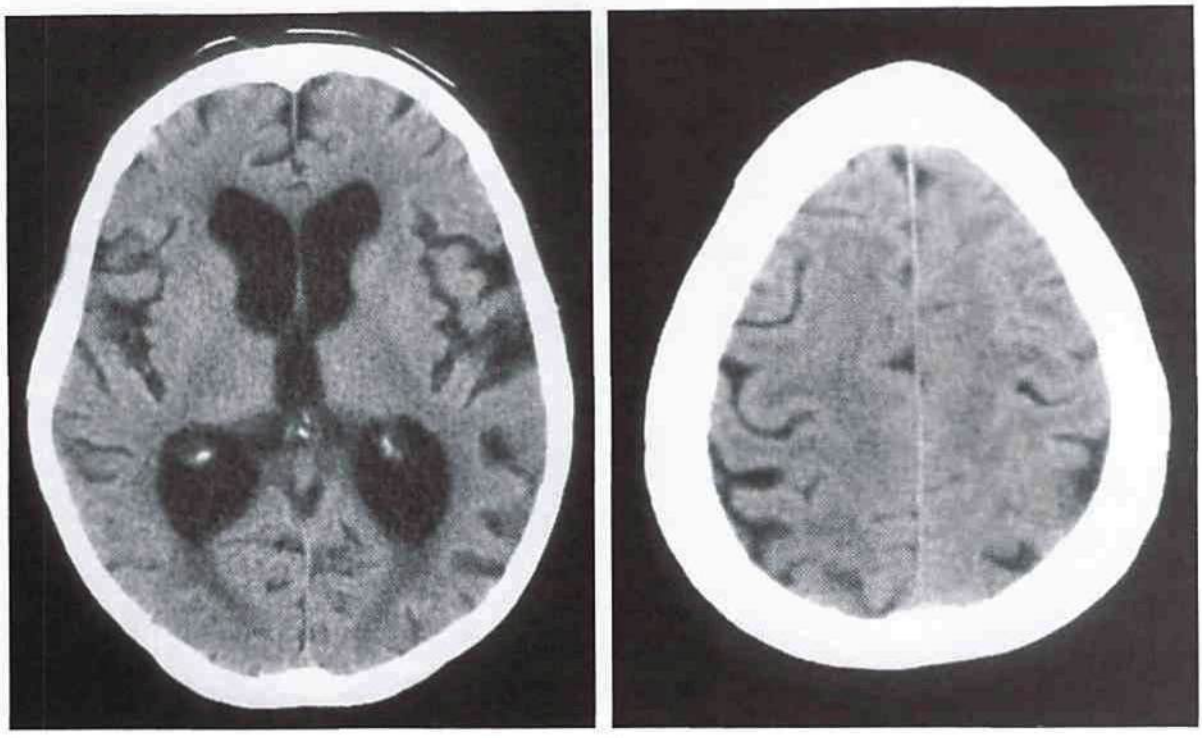


FIGURE 6-59. CT scan of a patient with normal pressure hydrocephalus. There is enlargement of all the ventricles, which is consistent with communicating hydrocephalus. In particular, the frontal horns of the lateral ventricles (A) are roughly disproportionate to the cortical atrophy (B). (Reproduced, with permission, from Ropper AH, Brown RH. *Adams and Victor's Neurology*, 8th ed. New York: McGraw-Hill, 2005: 536.)

TREATMENT

Shunt.

PROGNOSIS

Normalized ICP and ventricle size with improvement and reversal of symptoms.

MNEMONIC

Normal pressure hydrocephalus presents with a "wet, wacky, and wobbly" triad: incontinence, dementia, and ataxia.

CEREBROVASCULAR DISORDERS

Cerebrovascular disorders arise from any pathologic disorder in the blood vessels supplying the brain, such as occlusion by thrombus or embolus, increased vascular permeability, and vessel rupture (see Figure 6-60). The pathologic processes underlying these conditions manifest themselves clinically as ischemia with or without infarction, or hemorrhage. Strokes are the third leading cause of death behind myocardial infarctions and cancer.

PRESENTATION

Depends on the location of the cerebral lesion; see discussion of the different types below.

DIAGNOSIS

CT to detect hemorrhage/blood, diffusion tensor MRI to detect infarction.

MNEMONIC

To recall the blood supply from the vertebral artery superiorly, say the following three times fast: "PieKah, Eikah, Sicca, Picca" (PICA, AICA, SCA, PCA).

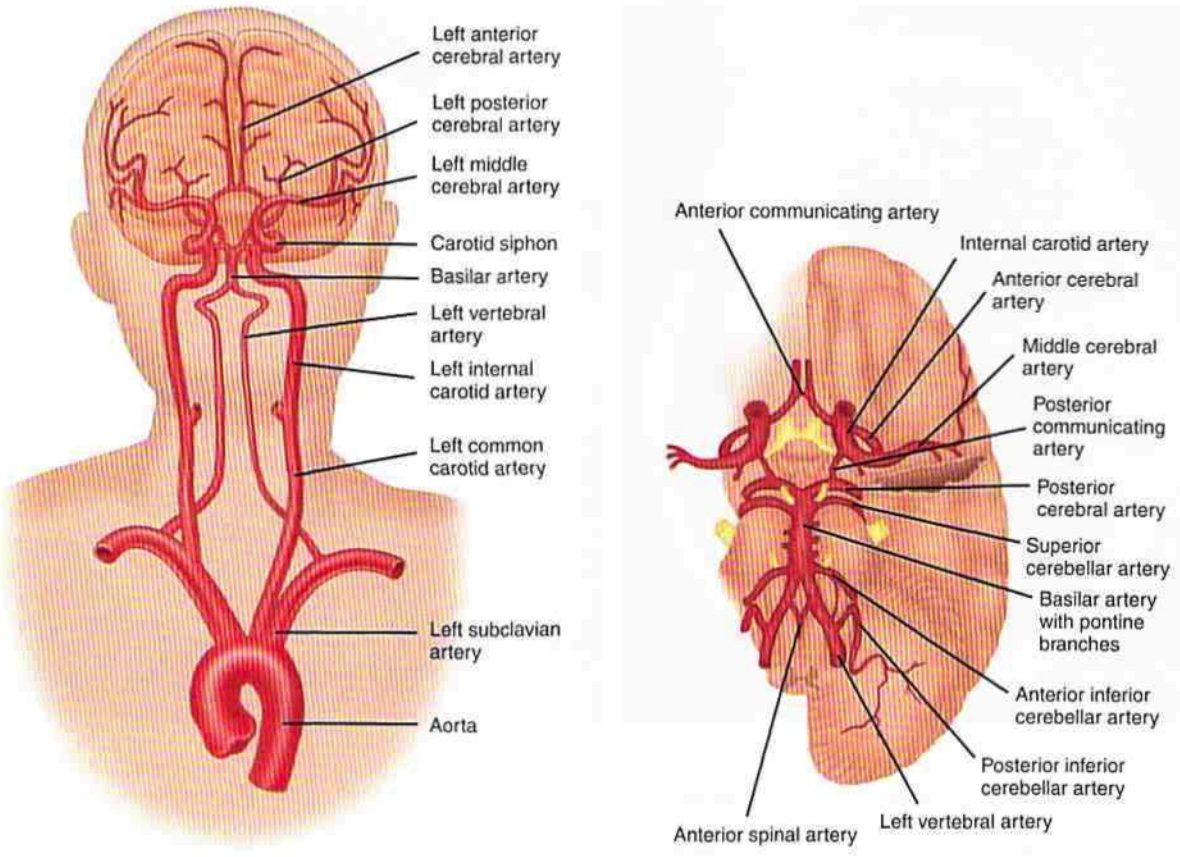


FIGURE 6-60. Schematic showing cerebral vasculature.

Thrombotic Stroke (Pale Infarction)

The most common type of stroke results from a platelet thrombus that forms over an inflammatory plaque in the MCA or internal carotid artery. This causes liquefactive necrosis that usually remains pale because of the lack of reperfusion.

Presentation

Grossly exhibits a wedge-shaped area of infarction that develops at the periphery of the cerebral cortex; 1–2 days postinfarction, edema develops, with loss of demarcation between the gray and white matter, with myelin breakdown. A cystic area and reactive gliosis (astrocytic proliferation at the margin of the infarct) occur in the weeks following the infarct. Clinically, transient ischemic attacks (< 24 hours) may precede the stroke.

Diagnosis

MRI; Symptoms consistent with middle or internal carotid artery distribution indicate where the infarct occurred,

Treatment

IV tPA within 3 hours of the onset of symptoms, rehabilitation therapy.

Embolic Stroke (Hemorrhagic Infarction)

Hemorrhagic infarction is thought to result from lysis of embolic material following arterial occlusion and ischemic necrosis that leads to partial restoration

of blood flow, which causes blood extravasation through the damaged vessel (reperfusion injury). Emboli originate most often from the heart or proximal atherosclerotic plaques in the carotid arteries.

Presentation

Grossly hemorrhagic infarcts extend to the periphery of the cerebral cortex in the distribution of the arterial supply. Clinically indistinguishable from a thrombotic stroke.

Diagnosis

CT or MRI.

KEY FACT

MRI is the imaging modality of choice for detection of ischemic brain injury, whereas CT will detect hemorrhage immediately.

Treatment

Treat underlying conditions predisposing to emboli: Atrial fibrillation, bacterial/nonbacterial endocarditis, or rheumatic heart disease. Anticoagulants (i.e., warfarin) are preventive. Rehabilitation therapy.

Intracranial Hemorrhage

These types of hemorrhage are best understood by their anatomic location and typical clinical presentation (see Table 6-25 and Figures 6-61 and 6-62).

KEY FACT

Vomiting at the onset of intracerebral hemorrhage occurs much more frequently than with infarction, and suggests bleeding as the cause of acute hemiparesis.

Binswanger Disease

Widespread degeneration of cerebral white matter occurs secondary to a vascular lesion (hypertension, atherosclerosis of small vessels, and multiple strokes).

Presentation

Dementia, gait disorder, and a pseudobulbar state, alone or in combination, in older patients with long-standing hypertension.

Diagnosis

Clinical findings and imaging.

Treatment

Treat the underlying hypertension.

Prognosis

Depends on the location of the infarction.

Lacunar Infarcts

Cystic areas of microinfarction result from hyaline arteriolosclerosis (small vessels) secondary to hypertension and diabetes mellitus (DM).

Presentation

- Pure sensory stroke when the infarct is in the ventrolateral thalamus.
- Pure motor hemiparesis from an infarct in the posterior limb of the internal capsule or basis pontis; the face, arm, and leg are almost always involved as opposed to the small MCA (face and arm worse than the leg) or ACA (leg worse than the face and arm).
- Ataxic hemiparesis from an infarct in the base of the pons.
- Dysarthria and a clumsy hand or arm due to infarction in the base of the pons or in the genu of the internal capsule.

TABLE 6-25. Types of Intracranial Hemorrhage

Hemorrhage	Etiology	Presentation	Treatment/Prognosis
Epidural	Rupture of middle meningeal artery following trauma (fracture) at pterion (temporparietal junction).	Loss of consciousness followed by lucid interval.	Unless hematoma clot evacuated urgently, will result in increased ICP, uncal herniation, and death due to respiratory arrest.
		Bradycardia with increased systolic pressure (Cushing effect).	Level of consciousness prior to surgery correlates with mortality (i.e., structures are already damaged if patient has significantly altered level of consciousness).
		CT is diagnostic and shows biconcave disk not crossing suture lines; arterial bleed creates blood between dura and bone that is limited by skull sutures (see Figure 6-61A).	
		Pressure on CN III parasympathetic portion results in blown pupil.	
Subdural	Rupture of bridging (emissary) veins between dural sinuses and arachnoid; often seen in shaken baby syndrome, alcoholics, and the elderly.	Venous bleeding (less pressure leads to slow expansion of hematoma) with a delayed onset of symptoms (days to weeks).	Removal of the hematoma by craniotomy is the treatment of choice.
	Predisposing factors include brain atrophy, shaking, whiplash.	Fluctuating level of consciousness that develops slowly, crescent-shaped hemorrhage that covers convexity of brain and crosses suture lines.	Without treatment, severe cerebral compression and displacement with temporal lobe–tentorial herniation can result in death.
Subarachnoid	Rupture of aneurysm (usually saccular/berry aneurysm) or an arteriovenous malformation that results in blood moving into the same spaces as the CSF (see Figure 6-62).	"Worst headache of my life," sudden-onset severe occipital headache.	Hemorrhage tends to recur at same site.
		Isolated CN III palsy with aneurysm at the junction of the PCA and internal carotid.	Surgical excision of aneurysm or fill with metal coil (prior to rupture).
		No single large clot and blood fills convexities and cisterns.	Level of consciousness at time of arteriography best index of prognosis.
		Bloody/xanthochromic spinal tap.	
		Impaired CSF resorption at the arachnoid granules resulting in communicating hydrocephalus(see Figure 6-61B).	
		Carotid and vertebral angiography only means of demonstrating aneurysm.	

TABLE 6-25. Types of Intracranial Hemorrhage *(continued)*

HEMORRHAGE	ETIOLOGY	PRESENTATION	TREATMENT/PROGNOSIS
Parenchymal	Hypertension, amyloid angiopathy, diabetes mellitus, and tumors.	Lateral striate artery hemorrhage secondary to hypertension affects the basal ganglia (putamen) (see Figure 6-61C) and thalamus (internal capsule), leading to hemiplegia, contralateral sensory loss (see Figure 6-61D); also affects pons/cerebellum, causing vomiting, inability to sit/stand/walk.	30%–35% patients die within 30 days.
	Pathology secondary to vascular changes related to hypertension leads to stress on penetrating vessels (lenitculo-striate vessels), then leads to Charcot-Bouchard macroaneurysm with vessel wall thickening.		Location largely impacts the prognosis along with the size of the hemorrhage.
	Ruptured aneurysms lead to intracerebral hemorrhage, which creates a clot that pushes the brain parenchyma aside.		Maintain adequate ventilation, monitor ICP.
			With sustained mean BP > 110 mmHg give β-blockers, ACE-inhibitors.
			Surgical evacuation of cerebellar hematomas.

- Pure motor hemiparesis with "motor (Broca's) aphasia" due to thrombotic occlusion of a lenticulostriate branch supplying the genu and the anterior limb of the internal capsule and adjacent white matter of the corona radiata.

DIAGNOSIS

Clinical signs/symptoms, imaging studies to exclude hemorrhage, X-ray cerebral angiography.

TREATMENT

Reduction in BP (statins, angiotensin-converting enzyme inhibitors), well-controlled DM, and aspirin.

PROGNOSIS

Generally fair to good. Depends on the location and extent of damage (as determined by PET scan, MR diffusion with MR perfusion to identify the ischemic penumbra, the area of ischemic tissue on the periphery of the infarct that will likely infarct).

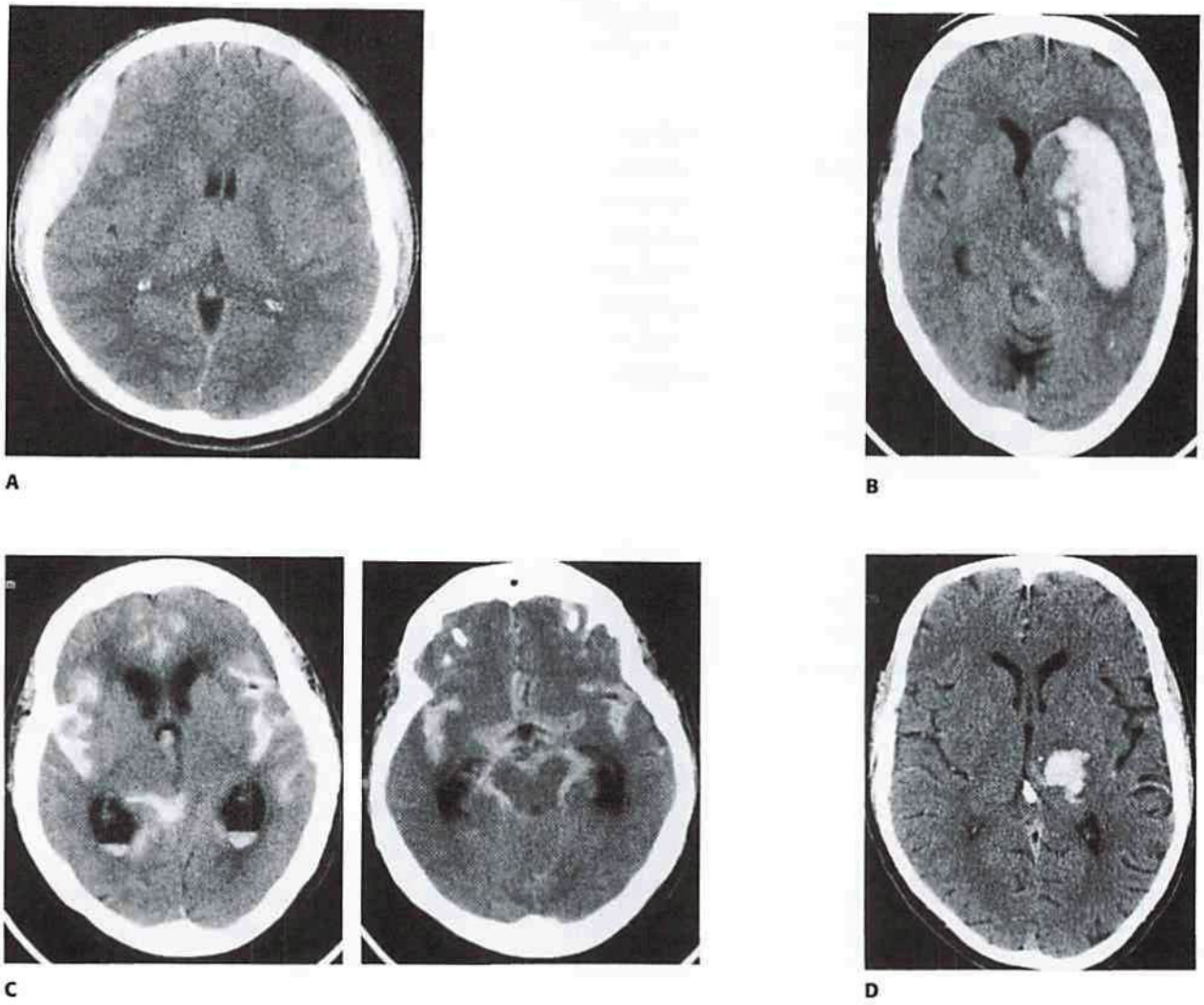


FIGURE 6-61. CT scans of intracranial hemorrhages. (A) Epidural, (B) subarachnoid, and (C, D) parenchymal hemorrhage. (Figure A reproduced, with permission, from Kasper DL, Braunwald E, Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 2450. Figures B–D reproduced, with permission, from Ropper AH, Brown RH. *Adams and Victor's Neurology*, 8th ed, New York: McGraw-Hill, 2005: 711, 713 and 719.)

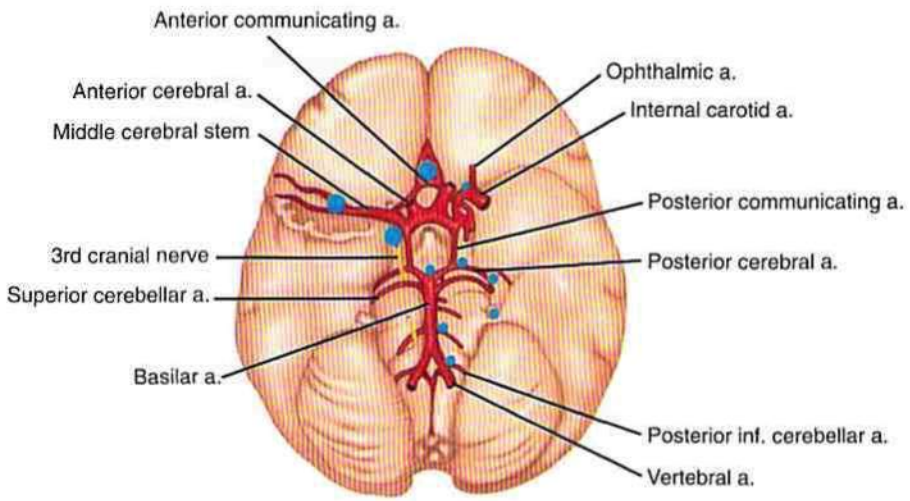


FIGURE 6-62. Principal sites of saccular aneurysms. Size of the circles is proportional to frequency at that site.

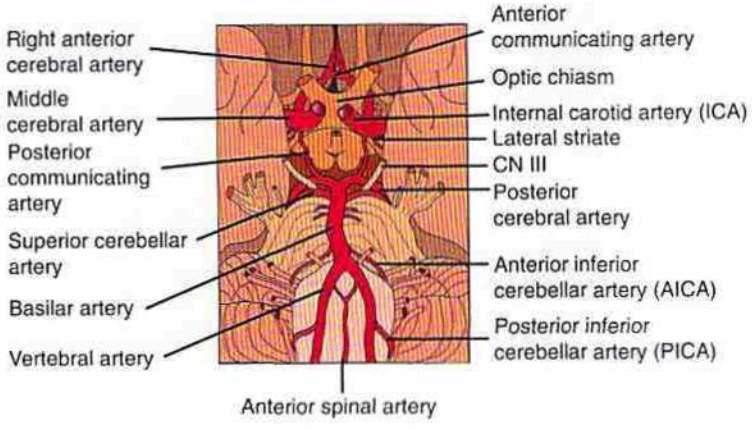


FIGURE 6-63. Diagram of the cerebral vasculature.

Stroke Presentation According to Cerebral Location of Occlusion

- **Middle cerebral artery** (see Figure 6-63)
  - Parietal lobe → contralateral hemianesthesia (face and arm worse than leg).
  - Frontal lobe → contralateral hemiplegia (face and arm worse than leg).
  - Temporal lobe → homonymous hemianopia.
    - If the **dominant hemisphere** is affected (usually left), aphasia will also develop.
    - If the **nondominant hemisphere** is affected (usually right), sensory neglect and apraxia will develop (no complex movements,inability to follow commands).
- **Anterior cerebral artery**
  - Parietal → contralateral hemianesthesia (leg worse than face or arm).
  - Frontal lobe → contralateral hemiplegia.
  - Medial frontal (midline) → urinary incontinence, re-emergence of the grasp reflex.
- **Posterior cerebral artery**
  - Occipital → homonymous hemianopia with macular sparing.
- **Anterior inferior cerebellar artery**
  - Ipsilateral loss of pain/temperature sensation (CN VII); hearing loss and nystagmus (CN VIII); ipsilateral dystaxia (inferior/middle cerebellar peduncle), which is difficulty controlling voluntary movements.

KEY FACT

Wallenberg's syndrome (lateral medullary infarct):
- Ipsilateral: Horner's syndrome, decreased corneal reflex and facial numbness (sensory V), ataxia and intention tremor (inferior cerebellar peduncle), palatal weakness and decreased gag reflex (nucleus accumbens), nystagmus (vestibular).
- Contralateral: STT lesion leading to hemisensory loss of pain and temperature sensation.

DYSKINESIAS

Disorders of movement involve disturbance of voluntary movement or the presence of involuntary movements, commonly referred to as **extrapyramidal** diseases because there is no muscle weakness (as is the case in UMN lesions). May arise from basal ganglia lesions and present as resting tremor, chorea, or athetosis. Other regions involved are the cerebellar hemisphere, cerebellar vermis, and subthalamic nucleus. Dyskinesias are symptoms that may be part of a syndrome or disease.

Chorea

Chorea is characterized by sudden, jerky, purposeless movements that arise from basal ganglia lesions.

MNEMONIC

Chorea = dancing (think **choreo**graphy).

KEY FACT

Athetos = not fixed (think snake-like).

KEY FACT

If a right-handed patient presents with aphasia, it can be confidently assumed that the lesion is in the left hemisphere. Imaging (CT/MRI) confirms the clinical suspicion.

KEY FACT

- Most individuals learn to read by transforming the printed word into the auditory form. Patients with Wernicke's aphasia may present with alexia because the auditory center for language (Wernicke's area) is damaged.
- Wernicke's aphasia is distinct from Wernicke-Korsakoff syndrome, a disease arising from thiamine deficiency (typically due to chronic alcohol abuse) that presents with encephalopathy, amnesia, ophthalmoplegia, and ataxia.

MNEMONIC

Broca's **Bro**ken **Bo**ca
Wernicke's is **W**ordy.

KEY FACT

Vascular dementia may be caused by:

- Multiple infarcts: Large-artery atherosclerosis in the circle of Willis and carotids.
- Binswanger's leukoencephalopathy: Loss of white matter secondary to hypertension-related atherosclerosis.
- Lacunar infarcts: Small 1-cm infarcts of the striatum and thalamus related to arteriosclerosis.

Diseases Characterized by Chorea

- **Inherited disorders**
  - Huntington's disease
  - Neuroacanthocytosis
  - Wilson's disease
- **Infectious**
  - Streptococcal infection (rheumatic fever).
- **Drug-induced chorea**
  - Neuroleptics (phenothiazines, haloperidol).
  - Phenytoin.
  - Oral contraceptives in women with systemic lupus erythematosus (SLE) and anti-phospholipid Ab.
  - Excessive dosage of L-dopa and dopamine agonists.
  - Cocaine.

Athetosis

An inability to maintain a body part in one position usually presents as slow, writhing movements (especially in the fingers) that alternate between extension and flexion. **Characteristic of a basal ganglia lesion.**

Hemiballismus

Sudden, uncontrolled flailing of one limb results from a lesion in the contralateral subthalamic nucleus.

Presentation

A lesion in the subthalamic nucleus releases the thalamus from inhibition by the globus pallidus internus → sudden uncontrolled flailing of the arm (continuous/intermittent).

Diagnosis

MRI showing signal changes in the contralateral subthalamic nucleus.

Treatment

Haloperidol, phenothiazine.

Prognosis

If hemiballismus persists for weeks without treatment, it may result in exhaustion and death.

APHASIAS

The muscles involved in generating speech, chewing, and swallowing are intact. Therefore, these patients do not have a peripheral motor problem, but rather one that arises from a cortical lesion. Speech therapy is recommended for all patients with aphasia (see Table 6-26).

DEGENERATIVE DISEASES

Degenerative diseases, as with other CNS disorders, are best understood by recognizing the deficits associated with the specific region in which the lesion develops (see Table 6-27).

TABLE 6-26. Perisylvian Types of Aphasias

Location	Presentation	Prognosis/Treatment
Broca's area (inferior fronatl gyrus)	▪ Motor/nonfluent/expressive aphasia with good comprehension, thus patient is aware of problem, and therefore will be extremely frustrated, cannot say what they are thinnking and use mainly short monosyllabic nonsensical words. ▪ Often accompaniedd by contralateral weakness (hemiparesis often on the right side) of the lower face and arm.	▪ May improve over time, excellent potential for functional recovery. ▪ Prognosis depends on the size of the lesion, the age of the patient, and the status of the contralateral hemisphere.
Wernicke's area (superior temporal gyrus)	▪ Sensory/fluent/auditory aphasia with impaired comprehension, neologisms, paraphasic errors, and impaired repetition. ▪ *Unaware of defect.* ▪ Often with contralateral visual defects (right upper quadrant loss because optic radiations from Meyer's loop are affected), alexia.	▪ May improve over time. ▪ Prognosis depends on the size of the lesion, *the age of the patient, and the status of the* contralateral hemisphere. ▪ Less likely to go back to social life because of severe comprehension defect.
Arcuate fasciculus	▪ Conduction aphasia because this structure connects Wernicke's to Broca's areas; poor repetition with intact comprehension and fluent speech. ▪ Cannot name objects.	▪ Prognosis depends on the size of the lesion, the age of the patient, and the status of the contralateral hemisphere.
Global	▪ Both speech and comprehension affected due to large *perisylvian or separate frontal and temporal.* ▪ Often accompanied by right hemiplegia, hemianesthesia, and homonymous hemianopia.	▪ May regain degree of comprehension. ▪ *Clinical picture may resemble Broca's aphasia* after time.

Generally, symptoms associated with diseases affecting the cerebrum include personality changes, memory loss, seizures, and cognitive dysfunction (see Tables 6-28).

Basal ganglia and spinocerebellar lesions generally present as movement disorders (see Table 6-29).

Spinocerebellar lesions affect the posterior column and present with ataxia (see Table 6-30.)



MNEMONIC

Treatment for Parkinson's is **BALSA:**
Bromocriptine
Amantadine
Levodopa (with carbidopa)
Selegiline (and catechol-O-methyltransferase inhibitors)
Anticholinergics

Progressive Supranuclear Palsy

Disease is characterized by widespread neuronal loss and subcortical gliosis that notably spares the cerebral and cerebellar cortices.



FLASH BACK

Wilson's *disease results from autosomal recessive mutations in a membrane-bound copper transporter that overwhelms copper capacity.*

Presentation

Onset in the sixth decade presenting with difficulty in vertical movement of gaze, pseudobulbar palsy (dysarthria, dysphagia, hyperactive jaw jerk and gag reflexes, and uncontrollable laughing or crying unrelated to emotional state), axial dystonia with repeated falls, and bradykinesia with memory and intellect intact.

Diagnosis

Exclusion of other causes, prominent neurofibrillary tangles.

TABLE 6-27. Motor Neuron Lesions

Types	Presentation	Pathology	Prognosis/ Treatment
Amyotrophic lateral sclerosis (ALS)	Associated with both LMN and UMN signs with sparing of sensation; onset at 40–60 years old; most common motor neuron disease; rare idiopathic form in 40 to 60 year olds (chromosome 21, SOD1 mutant).	UMN signs (spasticity, positive Babinski's sign).	No treatment, rapidly fatal due to respiratory failure.
	Thenar atrophy first sign (LMN lesion), fasciculations, hyperflexion (UMN lesion lateral corticospinal tract).	LMN signs (muscle weakness, denervation atrophy).	
Werdnig-Hoffman disease	Autosomal recessive inheritance that presents at birth as floppy baby, tongue fasciculations, LMN disease.	Degeneration of anterior horns; **no** UMN/corticospinal tract degeneration; congenital variant of ALS with only LMN signs.	Median age of death 7 years, rapidly fatal.
Poliomyelitis	Follows infection (fecal-oral) with poliovirus; first replicates in oropharnyx and SI before hematologic spread to CNS, presenting with LMN signs.	Degeneration of anterior horns of spinal cord.	Hospitalize with strict bed rest to reduce rate of paralysis. May develop new muscle weakness after recovery from acute paralytic poliomyelitis.
	CSF with lymphocytic pleocytosis and slight elevation of protein.		
	Virus recovered from stool or throat.		

KEY FACT

Parkinson's **disease** responds to treatment, whereas Parkinson's **syndromes** do not. Also there is genetic or idiopathic damage to the substantia nigra in the disease, while all the causes listed here relate to basal ganglia and the syndrome.

Treatment

No definitive treatment.

Prognosis

Death within 6 to 10 years.

DEMYELINATING DISEASES

Disease is characterized by the destruction of normal myelin (e.g., MS) or the production of abnormal myelin (e.g., leukodystrophy; see Table 6-31).

Multiple Sclerosis

KEY FACT

Cerebellar lesions (unilateral) present with ipsilateral ataxia, intention/movement tremor (difficulty smoothing movement), dysarthria (if in the lateral hemisphere, loss of complex movements of speech), and Romberg's sign (falling toward the affected side when the eyes are closed).

Multiple sclerosis is defined as an inflammatory autoimmune disorder characterized by autoantibodies directed against the myelin basic protein of oligodendrocytes in the CNS, which leads to periventricular demyelination of CNS axons (UMNs) of the brain and spinal cord. There is an increased prevalence in people who lived north of the Equator for the first decades of their lives. It most often affects Caucasian women 20–30 years old and is associated with HLA-DR2. MS is second only to trauma as a cause of neurologic disability in early to middle adulthood.

Presentation

Classic triad of scanning speech, intention tremor, and nystagmus, as well as UMN lesion signs (hyperreflexia). Is often relapsing-remitting. Optic neuritis,

TABLE 6-28. Cerebral Cortex Lesions

Types	Presentation	Pathology	Prognosis/Treatment
Alzheimer's disease	Slow, progressive mental deterioration with loss of short-term memory, anosmia, difficulties with language and planning skills.	Senile plaques (β-amyloid core surrounded by distended neurites containing tau, extracellular) that silver stain positive.	AchE inhibitors increase Ach and slow disease progression.
	Spares primary sensory and motor areas.	β-Amyloid is toxic when deposited in neurons, leads to weakening of cerebral blood vessel walls resulting in amyloid angiopathy and intracranial hemorrhage.	Survival 50% of expected rate secondary to cardiovascular and respiratory causes and inanition.
	Generalized cerebral atrophy beginning in temporal lobe and hippocampus leads to widened sulci, enlarged ventricles.	Decreased Ach because loss of cholinergic nuclei in forebrain (locus ceruleus, nucleus basalis of Meynert).	
	Tied with multi-infarct dementia as the most common cause of dementia in elderly.	Neurofibrillary tangles (intracellular, abnormally phosphorylated tau protein forming flame-shaped paired helical filaments twisted around each other).	
	β-Amyloid increases when defects in degradation of amyloid peptide precursor.		
	Familial form (10%) associated with onset at < 40 years and genes on chromosome 1 and 14 (presenelin 1 and 2 leads to hyperphosphorylated tau and neurofibrillary tangles), 19 (APOE4 allele), and 21 (p-*App* gene increases amount of amyloid peptide precursor amount, leading to increased production of β-amyloid, which explains Down's syndrome earlier onset and near 100% prevalence at age 30–40.		
Pick's disease	First sign is personality changes (disinhibition, dementia, impaired judgment) with language disturbance (aphasia).	Swollen neurons with Pick bodies (intracellular aggregated tau protein); straight filaments observed with silver staining.	Limited treatment options similar to Alzheimer's, targeting neurotransmitters.
	Aspects of Alzheimer's (memory loss) except with earlier age of onset (< 50 years), descent into the sea of mindlessness.	Loss of white matter underlying atrophic cortex, specific for frontal-temporal lobes, gliosis.	
Multi-infarct (vascular) dementia	Second most common cause of dementia.	Secondary to atherosclerosis.	Vascular prophylaxis and stroke prevention.
	A progressive, stepwise decline in functioning.		

TABLE 6-29. Basal Ganglia Lesions

Types	Presentation	Pathology	Prognosis/Treatment
Huntington's disease	Autosomal dominant with complete penetrance and development of progressive athetoid chorea in all four limbs (writhing), dementia, emotional disturbances, onset at 35–45 years with anticipation.	Atrophy of caudate nucleus leads to loss of GABAergic neurons.	Symptomatic treatment with haloperidol effective in suppressing movement disorder (care must be taken not to superimpose tardive dyskinesia; prescribe only for chorea that is functionally disabling).
	Atrophy of the caudate (head) and putamen may make lateral ventricles appear enlarged when imaging ("bat-wing" frontal horns).	Expansion of CAG repeats (polyglutamine) on chromosome 4 that results in aggregation of mutant huntingtin protein (toxic to neurons).	Incurable; steadily progressive course and death 15–20 years after onset with increased rate of suicide; requires supportive therapy and genetic counseling.
	Spared memory, increased blinking, impaired initiation and slowness of both pursuit and volitional saccadic movements and an inability to make a volitional saccade without movement of the head.		Length of repeat determines age of onset and severity (worse when inherited from affected father; allele more unstable during spermatogenesis leads to paternal expansion).
Parkinson's disease	Clinically defined by **TRAP-F: T**remor at rest (e.g., pill-rolling), cogwheel **R**igidity, **A**kinesia/bradykinesia, **P**ostural instability, **F**estinating gait, flat affect.	Lewy body inclusions (eosinophilic with halo, aggregate of β-synuclein representing damaged neurofilaments) diffusely in cortical neurons with few or no tangles or plaques.	Disease course 10–25 years.
	Rarely, linked to MPTP exposure (meperidine derivative [synthetic heroin]).	Depigmentation of the substantia nigra (secondary to loss of dopaminergic neurons).	Dopamine agonists, levadopa carry risk of drug-related dyskinesias.
	Arises from any insult that damages basal ganglia, including antipsychotics that are dopamine agonists, ischemia, chronic carbon monoxide poisoning, Wilson's disease, encephalitis.		Surgical intervention when positive response to levodopa; ablation/functional blockade (deep brain stimulation) of subthalamic nucleus effective at treating symptoms with no risk of drug-induced dyskinesias with long-term dopamine replacement therapy.

TABLE 6-29. Basal Ganglia Lesions *(continued)*

Types	Presentation	Pathology	Prognosis/Treatment
Wilson's disease	Onset at age 20–30 years, with asterixis, dystonia, tremor, and dementia preceded by liver cirrhosis, **greenish-brown pigmentation around iris** (Kayser-Fleischer rings in cornea).	Copper accumulation leads to a decrease in ceruloplasmin, increased urinary copper, causing degeneration of basal ganglia and clinical signs secondary to copper toxicity.	Zinc, penicillamine (copper chelator) + pyridoxine to prevent anemia effective at preventing progression of neurologic symptoms, low-copper diet.
		Liver biopsy and copper quantification is gold standard.	Liver transplantation curative for underlying metabolic defect.
Dementia with Lewy bodies	Extrapyramidal parkinsonian features because of loss of dopaminergic neurons, dementia, episodic delirium (visual hallucinations).	Widespread formation of Lewy bodies in substantia nigra, limbic, nucleus basalis of Meynert.	Selegiline, MAOI may be helpful.
	Undulating course.		Mortality eventually results from complications of immobility, poor nutrition, and swallowing difficulties.

TABLE 6-30. Spinocerebellar Lesions

Types	Presentation	Pathology	Prognosis/Treatment
Olivopontocerebellar atrophy	Loss of Purkinje cells leads to cerebellar lesion signs of ataxia (broad-based gait), dysarthria, intention tremor, generalized rigidity and dementia.	Loss of Purkinje cells (GABAergic in cerebellar cortex).	Progressive neurodegeneration with no definitive treatment.
		MRI shows flattening of pons, enlarged fourth ventricle. Alzheimer's disease inheritance.	Falls and aspiration pneumonia contribute to morbidity and mortality.
Friedreich's ataxia	Autosomal recessive trinucleotide repeat disease, with onset of symptoms in the first decade of life, presenting as a cerebellar lesion along with loss of proprioception resulting from destruction of dorsal root ganglion, decreased tendon reflexes, positive Babinski's sign.	"Atrophy of spinal cord," diffuse neuronal loss of posterior (DCT) white columns, spinocerebellar tract.	Poor prognosis, no definitive treatment.
	Most common hereditary ataxia; autosomal dominant inheritance.	Pathology mimics subacute combined degeneration of the spinal column.	
	Associated with myocarditis and hypertrophic cardiomyopathy.		

TABLE 6-31. Primary Characteristics of Demyelinating Disease

Types	Presentation	Pathology	Prognosis/ Treatment
Multiple sclerosis	Scanning speech, intention tremor and nystagmus; optic neuritis, transverse myelitis and MLF syndrome common.	Gliosis (chronic); macrophage (acute); periventricular demyelination.	Interferon beta.
Progressive multifocal leukoencephalopathy	Weakness, speech disturbance.	Infection of oligodendrocytes by JC virus.	Hospice care.

KEY FACT

Cerebellar hemispheres are laterally located, and control the lateral limbs; the vermis is centrally located, and lesions affect the central body. Therefore, cerebellar vermis lesions present with truncal ataxia, while hemispheric lesions present with intention tremor and limb ataxia.

FLASH BACK

Poliovirus is a picornavirus with single-stranded RNA and is icosahedral.

KEY FACT

Syringomyelia may also initially present with motor deficits, including thenar atrophy; however, in amyotrophic lateral sclerosis (ALS), afferent sensation is spared,

MNEMONIC

Triad of MS is a **SI(I)N:**
Scanning speech
Intention tremor
Internuclear ophthalmoplegia
Nystagmus

MLF syndrome/internuclear ophthalmoplegia (see MLF discussion below), paraplegia, hemiparesis, and hemisensory paresthesias.

Diagnosis

The diagnosis is made on the basis of the history and physical exam and must show evidence of multiple lesions occurring or worsening over multiple episodes. Labs may show increased polyclonal IgG (oligoclonal bands on electrophoresis), myelin basic protein, and leukocytes in the CSF. MRI shows multifocal plaques of periventricular demyelination in the white matter and correlates with future disease severity (see Figure 6-64). The acute lesion has macrophage infiltrates and $CD8^+$ T cells. The chronic lesion is characterized by gliosis (scarring).

Treatment

Interferon beta and immunosuppressive therapy have proven effective at improving disease severity and reducing relapse rates.

Prognosis

Untreated patients will develop severe physical disability within 20–25 years of onset. Early treatment may help counteract progressive brain atrophy.

Progressive Multifocal Leukoencephalopathy

A fatal subacute progressive demyelinating disease resulting from reactivation of latent John Cunningham (JC) infection of B lymphocytes (especially in AIDS patients) that pass through the BBB and cause eventual infection of oligodendrocytes. This leads to widespread destruction of white matter.

Presentation

Weakness and speech disturbance, with no change in mental status.

Diagnosis

MRI for white matter lesions. Eosinophilic intranuclear inclusions in oligodendrocytes.

Prognosis

Severe dementia, often progressing to death within 6 months to 1 year. Prognosis may be better in patients with higher $CD4^+$ lymphocyte counts.

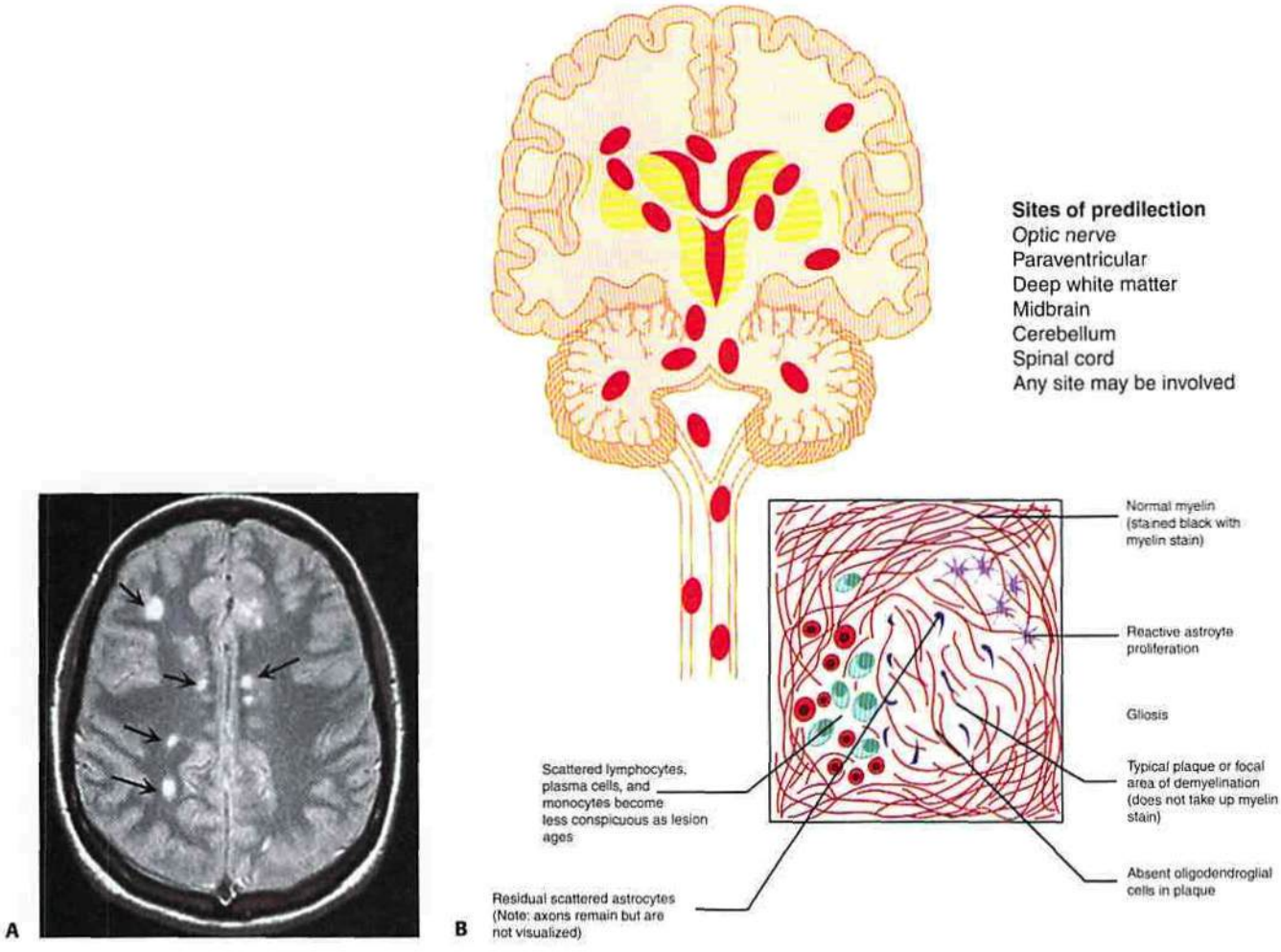


FIGURE 6-64. Multiple sclerosis. (A) Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. These demyelinating lesions may sometimes mimic brain tumors because of the associated edema and inflammation. (B) Common locations where plaques of demyelination occur and the histologic features of a plaque, including perivascular infiltration of inflammatory cells composed of activated T cells, B cells, and macrophages. (Figure A reproduced, with permission, from Kasper DL, Braunwald E, Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 2465. Figure B modified, with permission, from Chandrasoma P, Taylor CR. *Concise Pathology*, 3rd ed, New York: McGraw-Hill, 1998.)

Acute Disseminated (Postinfectious) Encephalomyelitis

Demyelinating disease follows infection with measles, mumps, rubella, and chickenpox, with a notable febrile prodrome. Distinct from **subacute** sclerosing panencephalitis by the timing of symptom onset. Specifically, the onset of acute postinfectious encephalomyelitis is much sooner than is the onset of the subacute variant.

Presentation

Seen in 11- to 12-year-olds with a history of recent infection or immunization presenting with abrupt onset of irritability and lethargy, mental status changes, and seizures.

Diagnosis

MRI, CSF to exclude other diagnoses; history of recent vaccination or exanthematous illness.

KEY FACT

Internuclear ophthalmoplegia results from a lesion of the MLF and is therefore also called MLF syndrome. When the affected eye is adducting, nystagmus is seen in the abducting opposite eye, indicating medial rectus palsy.

FLASH BACK

JC virus is a papovavirus that causes PML in patients with late-stage AIDS.

KEY FACT

Think of Guillain-Barré as MS of the PNS.

FLASH BACK

Metachromatic leukodystrophy is an autosomal recessive lysosomal storage disease (accumulation of sulfatides) that is fatal in the first decade and presents with progressive paralysis, dementia, and ataxia.

FLASH BACK

Krabbe's disease is an autosomal recessive disorder that leads to an accumulation of galactocerebroside in large, multinucleated histiocytic cells in the CNS. This results in optic atrophy and a classic presentation of blindness and peripheral neuropathy.

MNEMONIC

Krabbe's (crabs) cannot see and have poor sensation with their pincers (blindness and peripheral neuropathy).

KEY FACT

Viral infection of oligodendrocytes is the key feature of subacute sclerosing encephalitis (measles) and progressive multifocal leukoencephalopathy (JC virus).

KEY FACT

Adrenoleukodystrophy is an X-linked recessive enzyme deficiency in β-oxidation of fatty acids in peroxisomes that causes a build-up of long-chain fatty acids. This results in generalized loss of myelin in the brain, coupled with adrenal insufficiency.

Treatment

High-dose corticosteroids.

Prognosis

Complete recovery without apparent pathologic sequelae; degree of recovery is unrelated to severity of illness.

Guillain-Barré Syndrome

Inflammatory autoimmune demyelination of peripheral motor ventral roots and cranial nerves is often associated with infections. Guillain-Barré syndrome is associated with previous inoculation or infection (1–3 weeks earlier) by herpesvirus, *Campylobacter jejuni*, *Mycoplasma pneumoniae*, and possibly with flu vaccination. Notably, males and females are equally at risk. The autoimmune reaction is presumed to result from an immune response to non-self antigens that become misdirected against host nerve tissue.

Presentation

Presents **without fever.** Patients are areflexic, with rapidly evolving symmetric ascending muscle weakness and paresthesias that begin in the distal lower extremities. History of antecedent infection/inoculation. Significant risk of respiratory muscle paralysis over time. May have autonomic dysfunction → cardiac dysrhythmias, hypertension, hypotension. Facial diplegia (bilateral facial paralysis in 50% of cases). Deep, aching pain in weakened muscles.

Diagnosis

Clinical presentation, elevated CSF protein with normal cell count → papilledema. Abnormalities of nerve conduction by EMG.

Treatment

Respiratory support is critical, as the disease ascends to involve the diaphragm. Treatment also includes plasmapheresis and IV immune globulins once the diagnosis is made.

Prognosis

Death (< 5%) secondary to pulmonary complications within days; therefore, respiratory support is important. Most patients make a full recovery with supportive care. Prognosis is worse if axonal damage is evident.

Central Pontine Myelinolysis

Disease occurs in the hyponatremic (marathon runners who drink too much free water) and in patients who have had rapid IV correction of hyponatremia, thereby causing hypernatremia (i.e., liver transplant patients). In the CNS, this results in fluid moving from the neurons into the extracellular compartment, leading to a decrease in intracellular volume and subsequent demyelination.

Presentation

Rapid-onset quadriparesis with dysarthria/dysphagia.

Diagnosis

MRI shows a diamond-shaped or "bat wing" region of demyelination in the basis pontis that spares neurons and axons with no inflammation, distinguishing it from MS.

Treatment

Avoid by **slow** correction of hyponatremia (to avoid hypernatremia).

Prognosis

Maximum recovery within months; death is common.

SEIZURES

Seizures are characterized by focal or global neuronal hyperactivity that causes a sudden change in behavior. This change manifests differently, depending on the region of the brain affected (see Table 6-32).

TABLE 6-32. Types of Seizures

Type	Presentation	Treatment/ Prognosis	Etiology by Age
Partial (one area of the brain)	**Simple:** Consciousness intact with motor, sensory, autonomic, and psychic components.	Can secondarily generalize.	
	Complex: Components of simple without intact consciousness.	Carbamazepine for complex partial seizures.	
Generalized	Absence (petit mal). 2 years old to puberty with blank stare.	Do not treat absence seizures with sodium channel blockers, as they will worsen the seizure.	**Children:** Genetic, infection, trauma, congenital, metabolic. **Adults:** Tumors, trauma, stroke, infection. **Elderly:** Stroke, tumor, trauma, metabolic, infection.
	Myoclonic. Quick, repetitive jerks.		
	Tonic-clonic. Alternating stiffening and movement as it spreads across both hemispheres. Post-ictal phase leads to the recovery phase, with exhaustion and disorientation.		
	Tonic. Stiffening (usually in children).		
	Atonic. "Drop" seizures.		
May-White syndrome	Lipoma, ataxia, and deafness.	Familial progressive myoclonic epilepsy.	

KEY FACT

Physiologic myoclonus is characterized by sudden jerking movements while falling asleep.

FLASH FORWARD

Eating undercooked pork infected with *Taenia solium* may lead to neurocysticercosis. This is the leading cause of seizures in Mexico.

KEY FACT

Status epilepticus is defined by one or more seizures lasting more than 20 minutes without regaining consciousness. Typically, it presents as a tonic-clonic seizure characterized by sudden loss of consciousness, tonic contraction, and loss of postural muscles, followed by rhythmic contractions in all four limbs. Immediate treatment with clonazepam is needed to prevent anoxia and excitotoxic neuronal damage.

KEY FACT

An EEG spike-and-wave complex signifies increased hypersynchronicity and provides a useful tool to diagnose seizure.

KEY FACT

Patients with head trauma are intentionally hyperventilated to produce **respiratory alkalosis,** which causes cerebral vessel constriction by decreasing P_{CO_2}. This aims to decrease cerebral blood flow to decrease the risk of increased vessel permeability and cerebral edema.

KEY FACT

Respiratory acidosis causes increased vessel permeability, which enhances cerebral edema.

CEREBRAL EDEMA

An increase in ICP (i.e., intracranial hypertension) can occur 2–4 days postinfarction. Edema may be:

- **Intracellular:** Secondary to hypoxia and hyponatremia.
- **Extracellular:** Increased vascular permeability secondary to inflammation, metastasis, trauma, respiratory acidosis → space-occupying lesions that cause mass effect on underlying brain tissue.

Presentation

Classic signs of increased ICP → papilledema (swelling of the optic disk), projectile vomiting, sinus bradycardia, hypertension, and decreased level of consciousness.

Treatment

Address the underlying etiology if possible and manage ICP (shunt).

Prognosis

Potential for herniation; poor prognosis.

CEREBRAL CONTUSION

Permanent damage to small blood vessels and the surface of the brain, typically due to acceleration-deceleration injuries.

KEY FACT

Cushing's reflex is defined as bradycardia with hypertension secondary to cerebral ischemia. Both arms of the autonomic system are activated, with the sympathetic nervous system driving more blood centrally and baroreceptors activated to decrease heart rate.

Presentation

Coup (at the site of impact) and contrecoup (opposite the site of impact, usually at the tips of the frontal and temporal lobes) injuries. Contrecoup injuries are typically more devastating because of the increased forces necessary to transmit energy across the brain, resulting in diffuse axonal damage as well.

Diagnosis

CT or MRI.

Treatment

Rarely treated by surgery.

Prognosis

May progress to herniation as edema develops.

PRIMARY BRAIN NEOPLASMS

KEY FACT

Astrocytomas account for 70% of neuroglial tumors and are located in the frontal lobe of adults and the cerebellum in kids. The tumor grade determines the malignant potential.

KEY FACT

Glioblastoma multiforme is associated with Turcot's intestinal polyps.

Neoplasms may result in mass effect, which presents as seizures, dementia, focal lesions, increased ICP (headache worse in the morning, nausea, vomiting, and bradycardia with hypertension). Primary brain tumors seldom undergo metastasis. Most adult primary tumors are supratentorial, whereas the majority of childhood primary tumors are infratentorial (see Figure 6-65 and Table 6-33). Half of adult brain tumors are metastases from, in decreasing prevalence, lung, breast, melanoma skin, kidney, GI tract, and thyroid cancers. Metastatic brain lesions present as multiple spherical lesions at the gray-white junction that frequently bleed.

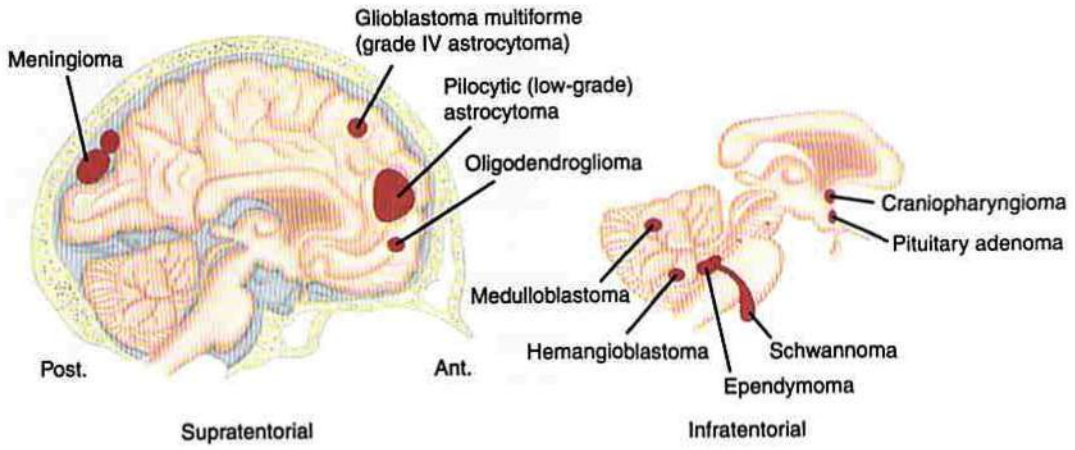


FIGURE 6-65. Location of adult and childhood primary brain neoplasms.

Pituitary Adenomas

Benign neoplasms arise from one of the five anterior pituitary cell types, and are generally monoclonal.

Presentation

Prolactin-secreting adenoma is the most common form. Compression of the optic chiasm and hypothalamic stalk/infundibulum (hyper- or hypopituitarism) leads to a classic presentation of daily headache and gynecomastia in males; secondary amenorrhea in females with galactorrhea is common.

Diagnosis

MRI, endocrine studies. Transsphenoidal surgery confirms the results of clinical and lab studies.

Treatment

Transsphenoidal surgery, normalization of excess pituitary secretion (dopamine agonists for prolactinomas).

Prognosis

If the lesion is resectable with preservation of pituitary function, then the prognosis is good.

SPINAL CORD LESIONS

See Tables 6-34, 6-35, and 6-36 and Figure 6-66.

Brown-Séquard Syndrome

Brown-Séquard syndrome results from hemisection of the spinal cord that interrupts conduction through the lateral corticospinal tract (CST, motor), lateral spinal thalamic tracts (STT, pain and temperature sensation), and dorsal columns (DC, proprioception and tactile sensation).

MNEMONIC

Bilateral hemianopsia resulting from sella turcica mass lesions, differential by age:
Adults → Pituitary **A**denoma
Kids → **K**raniopharyngioma

KEY FACT

Astrocytes can be visualized by staining for glial fibrillary acidic protein (GFAP).

KEY FACT

Meningiomas are associated with neurofibromatosis. Type II neurofibromatosis is associated with bilateral schwannomas.

KEY FACT

Psammoma bodies are associated with meningioma, papillary adenocarcinoma (thyroid), papillary cystadenocarcinoma (ovary), and mesothelioma.

TABLE 6-33. Primary Brain Neoplasms

	Type	Presentation and Pathology	Prognosis/Treatment
Adult peak incidence	Glioblastoma multiforme	"Pseudopalisading" tumor cells border central areas of **necrosis** and **hemorrhage**, with ring-enhancing appearance in imaging; found in cerebral hemispheres (frontal lobes most commonly) and may cross corpus callosum; ill-defined mass; most common primary brain tumor; high-grade astrocytoma.	< 1 year life expectancy, poor prognosis; seed neuraxis via CSF.
	Meningioma	Occurs in convexities of hemispheres and parasagittal region, leading to **spastic paresis and urinary incontinence;** arises from arachnoid cells external to the brain, may be resectable; symptoms arise from mass effect rather than infiltration of brain; spindle cells concentrically arranged in whorled pattern, psammoma bodies (laminated calcifications); **most common benign primary CNS tumor in adults;** common cause of new-onset focal seizures.	Resectable.
	Schwannoma-neurofibroma	Third most common primary brain tumor, benign; Schwann cell origin often localized to CN VIII at the cerebellopontine angle (vestibular schwannoma); may arise from any spinal root or CN except I and II (myelinated by oligodendrocytes); densely, uniformly-enhancing on MRI; present with progressive unilateral tinnitus, hearing loss, ataxia with positive Romberg's sign (because localized at cerebellopontine angle); commonly occurs in neurofibromatosis II.	Resectable; may preserve hearing if small and prevent compression of cerebellum, pons, and facial nerve; patient usually deaf at presentation.
	Oligodendroglioma	**Slow growing,** rare tumor most often in frontal lobes; **"fried egg" cells** with round nuclei with clear cytoplasm; often calcified.	Surgical resection.
	Pinealoma Pituitary adenomas (see section above)	50% are germinomas that occur more often in males < 30 years old with symptoms similar to pure pineal gland tumor without melatonin abnormalities; pineal gland tumors compress superior colliculus, pretectal area, and cerebral aqueduct (obstructive hydrocephalus); also interrupt melatonin production, leading to disruption circadian of rhythm, insomnia; may calcify with age; precocious puberty.	Surgical resection.
Childhood peak incidence	Pilocytic	Diffusely infiltrating benign glioma most often seen in posterior fossa (cerebellar); Rosenthal fibers (eosinophillic corkscrew fibers resulting from accumulation of α β crystalline specific to astrocytes); cyst with mural nodule.	Good prognosis.
	Medulloblastoma	Highly malignant tumor with rosettes or perivascular pseudorosette pattern of cells; arises in cerebellar vermis; small, basophilic cells; presents with ataxia, projectile vomiting, nuchal rigidity; can compress fourth ventricle leading to hydrocephalus and increased ICP.	Radiosensitive, may progress to cerebellar herniation without surgery.

TABLE 6-33. Primary Brain Neoplasms *(continued)*

	Type	Presentation and Pathology	Prognosis/Treatment
Childhood peak incidence *(continued)*	Ependymoma	Ependymal cell tumors most commonly found in fourth ventricle; characteristic perivascular pseudorosettes (ependymal cells around small vessels); rod shaped blepharoplasts (basal ciliary bodies) found near nucleus; can cause hydrocephalus (nausea, vomiting, nuchal rigidity, increased ICP).	Poor prognosis.
	Hemangioblastoma	Associated with von Hippel–Lindau syndrome when found with retinal angiomas; foamy cells and high vascularity are characteristic; may produce erythropoietin, causing secondary *polycythemia; mesodermal origin.*	Resection.
	Craniopharyngioma	Most common childhood supratentorial tumor, benign; derived from remnants of Rathke's pouch (ectoderm resembling tooth enamel [ameloblasts]); distinguish from pituitary adenoma by histology (nests of uniform granular cells); present with growth failure, papilledema; compression of pituitary stalk leads to hypopituitarism, while compression of optic chiasm leads to bitemporal hemianopsia.	Resection.
	Retinoblastoma	Malignant retinal tumor of childhood; sporadic; is generally unilateral, whereas bilateral suggests *rb* gene deletion; two-hit hypothesis prototype.	Radiotherapy, cryotherapy, chemotherapy, or enucleation.

TABLE 6-34. Comparison of Lower and Upper Motor Neuron Lesions

Motor Neuron Signs	Upper Motor Neuron (UMN)	Lower Motor Neuron (LMN)
Weakness	+	+
Atrophy	–	+
Fasciculation	–	+
Reflexes	↑	↓
Tone	↑	↓
Babinski	+	–

Nerves that run from the brain to the spinal cord originate from upper motor neuron (UMN); nerves that run from the spine to periphery originate from lower motor neuron (LMN).

KEY FACT

Ependymoma arises in the cauda equina in adults.

KEY FACT

Choroid plexus papillomas occur in the lateral ventricles of boys.

KEY FACT

Subependymal giant cell astrocytoma is pathognomonic for tuberous sclerosis (also with cardiac myomas and renal angiomyolipomas).

MNEMONIC

Randy **T**ravis **D**rinks **C**old **B**eer:
Roots
Trunks
Divisions
Cords
Branches

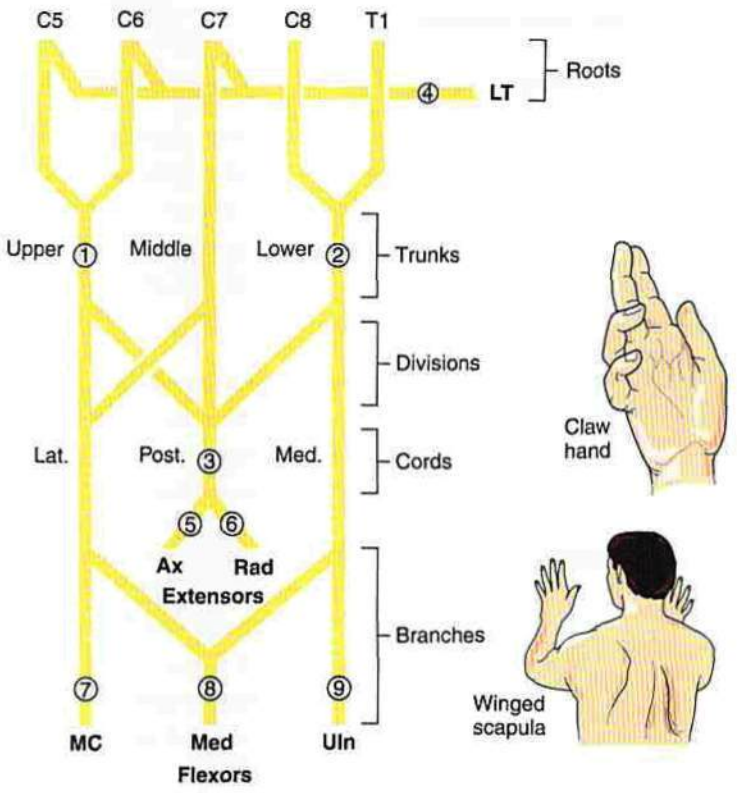


FIGURE 6-66. Diagram of the brachial plexus and associated presentation of lesions. Rad = radial nerve; Ax = axillary nerve; LT = long thoracic nerve; MC = musculocutaneous nerve; Med = median nerve; Uln = ulnar nerve. 1. Waiter's tip (Erb's palsy); 2. Claw hand (Klumpke's palsy); 3. Wrist drop; 4. Winged scapula; 5. Deltoid paralysis; 6. Saturday night palsy (wrist drop); 7. Difficulty flexing elbow, variable sensory loss; 8. Decreased thumb function, Pope's blessing; 9. Intrinsic muscles of hand, claw hand.

KEY FACT

CNS lymphomas generally result from metastasis of high-grade non-Hodgkin's lymphoma of B-cell origin.

PRESENTATION

- **Ipsilateral** UMN signs below the lesion (CST).
- **Ipsilateral** loss of tactile, vibration, and proprioception (DC) at and below the lesion.
- **Contralateral** loss of pain and temperature below the lesion (because of crossing fibers, STT).
- **Ipsilateral** loss of pain and temperature at the level of the lesion.
- LMN signs at the level of the lesion.
- If the lesion is above T1, patient may present with Horner's syndrome.

DIAGNOSIS

History and physical exam.

TREATMENT

Early treatment with high-dose steroids has shown benefit, as have physical therapy and surgery.

PROGNOSIS

Poor; depends on the etiology of the syndrome (trauma, infection, disk herniation).

TABLE 6-35. Upper Extremity Nerve Injury

Nerve	Site of Injury/Deficit in Motion	Deficits in Sensation/Course
Radial (C5–C8)	**Shaft of humerus,** leading to loss of triceps brachii, brachioradialis, and extensor carpi radialis.	Posterior brachial cutaneous, also involved in lateral epicondylitis ("tennis elbow").
Median (C5–C11)	**Supracondyle of humerus** leaving arm muscle power intact with loss of forearm pronation, wrist flexion (with ulnar deviation), finger flexion, thumb abduction and apposition, thenar atrophy.	Loss of sensation over the lateral palm, thumb and radial 2.5 fingers, and thumbnail bed.
	Carpal tunnel syndrome (repetitive use injury).	Passes through pronator teres, under flexor retinaculum in carpal tunnel.
	Slashing the wrist causes loss of thenar muscle innervation, so thumb movement is lost except for adduction.	Tinel's sign (shock-like pain when lightly tapped on underside of wrist) and Phalen's sign (wrist in flexion reproduces painful symptoms).
Ulnar (C8–T1)	**Medial epicondyle** causing impaired wrist flexion and adduction, impaired adduction of thumb and ulnar two fingers (claw-hand deformity), and wasting of hypothenar eminence and PAD/DAB muscles.	Loss of sensation over medial palm and ulnar 1.5 fingers.
		Passes through carpi ulnaris, at elbow; passes between medial epicondyle and two heads of flexor carpi ulnaris.
Axillary (C5 and C6)	**Surgical neck of humerus or anterior shoulder dislocation** causes loss of deltoid action (failure to abduct arm > 15 degrees).	**On physical exam,** palpable depression under acromion.
Musculocutaneous (C5–C6)	Loss of function of coracobrachialis, biceps, and brachialis muscles, along with decreased supination.	Passes through coracobrachialis and continues as lateral cutaneous nerve of forearm below elbow.

Poliomyelitis

Destruction of the anterior horn of the spinal cord occurs secondary to fecal-oral infection by poliovirus (a picornavirus) and leads to LMN destruction (see Figure 6-43). Poliovirus replicates in the orophaynx and small intestine before spreading through the bloodstream to the CNS.

FLASH BACK

Primary CNS lymphoma is associated with AIDS. EBV-mediated B-cell lymphoma is the most common cerebral tumor in AIDS patients. MRI showing a single ring-enhancing lesion distinguishes it from toxoplasmosis (multiple lesions).

FLASH BACK

In contrast to **craniopharyngiomas** (which arise from the remnant Rathke's pouch and create symptoms by interruption of the infundibulum connecting the hypothalamus to the pituitary), **pituitary adenomas** arise from cells within the pituitary gland itself, with symptoms resulting from a combination of aberrant tumor cell hormone secretion and mass effect.

KEY FACT

Familial syndromes associated with pituitary adenomas include multiple endocrine neoplasia (MEN 1), McCune-Albright syndrome, and familial acromegaly.

MNEMONIC

Lower MN = everything **lowered** (less muscle mass, decreased tone, decreased reflexes, downgoing toes).

Upper MN = everything **up** (tone, reflexes, and toes, and positive Babinski's sign).

TABLE 6-36. Lower Extremity Nerve Injury

Nerve	Deficit in Motion	Deficits in Sensation/ Course
Common peroneal (L4–S2) (divides into superficial and deep branches at the neck of fibula)	Loss of dorsiflexion, causing foot drop.	**Anterior compartment syndrome** results from increased pressure that causes compression of the deep peroneal nerve and vasculature, causing foot drop and weak dorsalis pedis pulse.
	Deep peroneal: Innervates muscles of anterior compartment, first web space sensation.	
	Superficial peroneal: Innervates lateral compartment muscle.	
Tibial (L4–S3) (courses inferior to the lateral malleolus)	Loss of plantarflexion because the tibial nerve innervates the posterior compartment of the thigh and leg.	Plantar surface of foot.
Femoral (L2–L4)	Loss of knee extension/knee jerk.	Paresthesias of anterior thigh and medial leg.
Obturator (L2–L4) (exits through the obturator canal to enter the thigh)	Loss of hip adduction.	

KEY FACT

Multiple sclerosis exhibits random and asymmetric lesions due to demyelination, mostly in the white matter of the thoracic and cervical regions, which results in a combination of motor and sensory deficits. The most common presentation with spinal cord lesions is episodic paraparesis.

KEY FACT

Loss of CST leads to muscle atrophy. ALS is rapidly fatal secondary to respiratory muscle failure.

KEY FACT

Spinal artery infarction (anterior/ventral arteries are more susceptible because of sparse collaterals) presents with:

- Bilateral loss of pain and temperature (STT).
- Bilateral spastic paresis (CST).
- Flaccid paralysis (LMN).

Loss of bladder control results from loss of CST innervation in the S2–S4 parasympathetic fibers. If the infarction is above T2, presents as Horner's syndrome. The dorsal columns and tract of Lissauer (tract in which the STT travels superior and inferior) are spared,

KEY FACT

Diabetic polyradiculopathy mimics tabes dorsalis.

Presentation

Malaise, headache, fever, nausea, abdominal pain, and sore throat characterize the acute infection. **Signs of LMN lesion** include muscle atrophy, flaccid paralysis, and hyporeflexia, with preserved sensation.

Diagnosis

CSF with lymphocytic pleocytosis, with slight elevation of protein. Virus is recovered from stool or the throat.

Treatment

Prevention with vaccine (Salk inactive parenteral vaccine). Oral vaccines carry the risk of disease. Bed rest decreases the incidence of paralysis; intensive care is needed if respiratory muscle weakness occurs.

Prognosis

High mortality rate if bulbar; persistent muscle weakness may develop years after acute infection.

Tabes Dorsalis (Tertiary Syphilis)

Degeneration of the dorsal roots and columns (mainly lumbosacral) that develops 15–20 years after the onset of infection. Primarily affects the fasciculi gracilis bilaterally.

Presentation

Ataxia, bilaterally impaired proprioception, paresthesias (lightning-like pains), Argyll Robertson pupils (accommodate, but do not react), and absence of

deep tendon reflexes. Purely sensory deficit; muscular power is retained, Associated with Charcot's joints (insensitivity to pain in the joint, leading to increased susceptibility to future injury to the joint).

Diagnosis

Clinical and CSF analysis (VDRL).

Treatment

Penicillin; treat symptoms after infection (nonantisyphilitic medications).

Prognosis

May have residual symptoms.

Subacute Combined Degeneration (Vitamin B_{12} Deficiency)

Demyelination of the dorsal columns and lateral CST occurs (when symptoms present in the lower limbs). Generally results from a failure to absorb vitamin B_{12} across the intestinal mucosa, which leads to a functional vitamin B_{12} deficiency leading to a build-up of methylmalonyl-CoA and its precursor, propionyl-CoA. Propionyl-CoA displaces succinyl-CoA in fatty acid synthesis, resulting in anomalous insertion of odd-chain fatty acids into lipids, such as myelin.

KEY FACT

Vitamin B_{12} deficiency also may result in pernicious anemia (macrocytic RBC).

Presentation

Dementia, ataxic gait, hyperreflexia (demyelinated CST leads to UMN loss), and bilateral loss of DCT and CST (symmetric spastic paresis); impaired position and vibration sense.

FLASH BACK

Methylated B_{12} (cobalamin) is an essential cofactor for the conversion of homocysteine to methionine, so deficiency results in impairment of DNA synthesis, resulting in pernicious anemia.

Diagnosis

Serum cobalamin, MRI, positive Schilling test.

Treatment

Vitamin B_{12} supplements (oral, intramuscular).

Prognosis

Best prognosis is in those with gait disturbance less than 3 months prior to commencement of treatment.

KEY FACT

The patient with syringomyelia classically presents after repeatedly burning their hand on the stove due to loss of pain and temperature sensation.

Syringomyelia

Enlargement of the central canal of the spinal cord leads to damage of the STT fibers (anterior commissure). May also erode the anterior horn, resulting in motor defects. Often presents in patients with Arnold-Chiari malformation (herniation of the cerebellar vermis through the foramen magnum, causing hydrocephalus, meningomyelocele, and platybasia).

KEY FACT

The sciatic nerve (L4–S3) emerges at the midpoint between the greater trochanter and the ischial tuberosity, important landmarks for gluteal injections, then branches into the tibial and common peroneal nerves at the short head of the biceps femoris.

Presentation

Bilateral loss of pain and temperature sensation in the upper extremities (most often at C8–T1 ["cape and shawl" distribution]) with preservation of touch sensation. LMN signs of flaccid paralysis if the anterior horn cells are affected, causing combined sensory and motor defects. Atrophy of hand interossei.

Diagnosis

Distinguish from ALS (thenar atrophy), because patients present with motor and sensory deficits; MRI is diagnostic.

MNEMONIC

Radial nerve innervates the **BEST:**
Brachioradialis
Extensors
Supinator
Triceps

KEY FACT

Patients with DM may develop peripheral neuropathy secondary to osmotic damage to Schwann cells. This is the most common cause of peripheral sensory and motor axonopathy; for this reason, it is extremely important to check the feet of diabetic patients!

KEY FACT

Toxin-associated peripheral neuropathy results from alcohol abuse, exposure to heavy metals, and diphtheria.

KEY FACT

Idiopathic Bell's palsy and Guillain–Barré syndrome are other examples of diseases affecting the PNS.

KEY FACT

Midbrain lesions
- Medial: Ipsilateral CN III palsy, contralateral hemiplegia.
- Lateral: Ipsilateral CN III palsy, contralateral cerebellar dystaxia with intention tremor, and loss of tactile sensation in the trunk and extremities.
- Tectal (dorsal): Failure of upward gaze (Parinaud's syndrome).

Ventral pons lesion: "Locked-in syndrome," in which only vertical eye movement and eyelid elevation are intact. Results from a lesion of the CST and corticobulbar tract.

Treatment

With Arnold-Chiari malformation, place shunt to decrease hydrocephalus before correction of syrinx (posterior fossa decompression).

Prognosis

Poor.

Thoracic Outlet Syndrome (Klumpke's Palsy)

An embryologic defect (cervical rib) can compress the subclavian artery and the inferior trunk of the brachial plexus (C8, T1). Also observed in weightlifters (hypertrophy of the anterior scalene muscle compresses the neurovascular bundle that runs between the anterior and middle scalene muscles), or hyperabduction of the arm (as in falling, breech birth).

Presentation

Thenar and hypothenar eminence (median nerve) atrophy, atrophy of the interosseous muscles, and sensory deficits on the medial side of the forearm and hand. Disappearance of the radial pulse when the head is rotated toward the opposite side due to compression of the subclavian artery.

Diagnosis

History, physical exam, and chest X-ray demonstrating cervical rib.

Treatment

Anterior scalenectomy (careful to avoid the phrenic nerve that runs on the anterior scalene deep to the prevertebral fascia); physical therapy.

Prognosis

Symptoms may return following treatment secondary to scarring and fibrosis around the nerve roots.

PERIPHERAL NEUROPATHY

Two types occur:
- Demyelination often presents segmentally with sensory changes (discrete sensory loss following the distribution of one or more nerves).
- Axonal degeneration of motor nerves presents as muscle fasciculation leading to muscle atrophy. Axonal degeneration of sensory nerves occurs first (small fibers [pain and temperature] are more prone to damage), and presents with a "**stocking-and-glove**" distribution (longer fibers are more prone to damage).

Charcot-Marie-Tooth Disease

The most common hereditary neuropathy (autosomal dominant); affects the peroneal nerve primarily; onset is primarily in the first or second decade.

Presentation

Peroneal nerve neuropathy leading to atrophy of the lower leg muscles. This results in an "inverted bottle" appearance of the legs.

Diagnosis

History and physical exam.

Treatment

No therapy to prevent onset or delay progression; patients may benefit from physical therapy and surgery for contractures.

Prognosis

No cure; progressive peripheral neuropathy.

CRANIAL NERVE PALSY

Cranial nerves arise from their nuclei in the brain stem and course toward their targets, primarily in the face. Muscles of facial expression, mastication, autonomic functions, and special sensory fibers are supplied by these nerves. Defects result either when the nucleus or the fiber is damaged, and may be bilateral or unilateral, depending on the degree of damage to the cortical collateral pathways; unilateral defects commonly present with lesions closer to the periphery (see Table 6-37).

Defects in Eye Movement

CN III Lesion

Presentation

Lesion causes the eye to point "down and out" (only the lateral rectus and superior oblique are functional), in addition to severe ptosis (as opposed to Horner's syndrome, which is mild ptosis).

Etiology

- Posterior cerebral artery aneurysm compresses the nerve, which causes a fixed, dilated pupil because pupillary fibers run along the periphery of the nerve bundle.
- Weber's syndrome: Midbrain tegmentum lesion causing ipsilateral CN III palsy and contralateral body hemiplegia.
- Diabetic CN III palsy spares the pupil because it is an ischemic rather than a compressive lesion. Pupillary fibers run on the surface of the nerve, so they are the first to be involved in compression and the last to be involved in ischemia.

Diagnosis

Physical exam.

Treatment

Watchful waiting or treatment of the underlying condition (e.g., surgical clipping of an aneurysm).

Prognosis

Most resolve within 6–8 weeks.

CN IV Lesion

Eye rotated superior and lateral because of unopposed action of the inferior oblique.

Etiology

Compression within the cavernous sinus (as with an internal carotid aneurysm).

KEY FACT

Medial inferior pontine syndrome: Ipsilateral lateral rectus paralysis (CN VI lesion) with contralateral spastic hemiparesis and loss of pain and temperature sensation.

KEY FACT

Bilateral Bell's palsy is almost always the result of Lyme disease.

KEY FACT

Fibers to the upper facial muscles receive bilateral corticobulbar innervation, which explains why UMN lesions of CN VII present only with lower facial paralysis. Fibers to the lower face muscles are only innervated by the contralateral cortex.

KEY FACT

Trigeminal neuralgia (tic douloureux) presents as severe stabbing pain in the sensory distribution of CN V. If present in a young person, it almost always indicates MS.

KEY FACT

CN IV (trochlear nerve) is the only cranial nerve to cross the midline; therefore, a lesion at the nucleus will result in the contralateral eye deviating superiorly and laterally.

KEY FACT

Cavernous sinus syndrome results from internal carotid aneurysm (mass effect) that presents as ophthalmoplegia and ophthalmic and maxillary sensory loss (CN V1 and V2).

TABLE 6-37. Cranial Nerve Palsy

TYPE/LOCATION	PRESENTATION	ETIOLOGY/NOTES
CN III, CN IV	(See below).	(See below).
	Anhidrosis (absence of sweating).	
	Miosis (pupil constriction).	
CN VII (Bell's palsy)	Drooping corner of mouth with drooling; loss of buccinator muscle function.	Complete destruction of facial nucleus or its branchial efferent fibers (facial nerve, CN VII).
	Difficulty speaking, inability to close eye.	Idiopathic (gradual recovery).
	Loss of taste in anterior two-thirds of tongue (chorda tympani).	Seen in AIDS, Lyme disease, sarcoidosis, tumors, and diabetes.
	Loss of lacrimation and salivation.	
	Peripheral lesions can be distinguished from central (nuclear) lesions by unilateral loss of all muscles of facial expression, compared to central presentation of bilateral innervation to frontalis.	
CN XII lesion (LMN)	Tongue deviates toward side of lesion ("lick your wounds").	Anterior spinal artery infarct.
CN V motor lesion	Jaw deviates toward side of lesion.	If lesion at trigeminal nucleus, then ipsilateral loss.
		If lesion higher up in thalamus and cortex, then contralateral signs.
CN X lesion	Uvula deviates away from side of lesion.	Brain stem infarct.
CN XI lesion	Weakness turning head to side contralateral to lesion; shoulder droop on side of lesion.	Sternocleidomastoid (SCM) contraction normally moves head to contralateral side.
		Loss of SCM and trapezius innervation accounts for presentation.
Parinaud's syndrome	Bilateral paralysis of upward gaze.	Midbrain dorsal tectum lesion **(pineal gland tumor)** that compresses superior colliculus, pretectal area, and cerebral aqueduct (obstructive hydrocephalus); also interrupts melatonin production, leading to disruption of circadian rhythm, insomnia; may calcify with age, precocious puberty.

DIAGNOSIS

Physical exam, imaging to detect underlying etiology.

TREATMENT

Surgical intervention.

Prognosis

Most resolve completely within 6 months.

CN VI Lesion

Affected eye fails to abduct; unaffected eye develops nystagmus when the patient tries to abduct the affected eye.

Etiology

Lesion within the cavernous sinus or pontomedullary junction; increased ICP, causing a downward shift in the posterior fossa.

Diagnosis

Physical exam and imaging.

Treatment

Watchful waiting.

Prognosis

Most resolve within 6 months.

Facial Lesions

UMN Lesion

- Lesion of the motor cortex or the connection between the cortex and the facial nucleus → contralateral paralysis of the lower face only.

LMN Lesion

- Ipsilateral paralysis of the upper and lower face.

Bell's Palsy (See Table 6-37)

Visual Field Defects

Lesions occurring anywhere from the retina to the visual cortex result in defects in the visual field (see Figure 6-48). The specific intervention depends on the underlying etiology and whether the lesion is a severed tract or a parenchymal injury.

Uveitis

Presentation

Blurry vision (resulting from inflammation of the iris, ciliary body, and choroids) may lead to retinal detachment and acute glaucoma.

Associated with:

- **Autoinflammatory disease:** Ankylosing spondylitis, Reiter's syndrome, sarcoidosis, ulcerative colitis.
- **Infection:** Toxoplasmosis, CMV, toxocariasis (ocular larval migrans), histoplasmosis, TB, syphilis.

Internuclear Ophthalmoplegia (Medial Longitudinal Fasciculus Syndrome)

Lesion of the MLF results in medial rectus palsy on attempted lateral gaze. This lesion is distinguished from CN III palsy by preserved convergence, in contrast to the "down and out" appearance of CN III palsy. Most common cause is MS.

KEY FACT

Signs suggestive of brain stem lesions: vertigo (CN VIII), diplopia (CN III, IV, VI), ataxia (cerebellar), perioral numbness (CN V), loss of consciousness (RAS).

KEY FACT

Argyll Robertson pupil, seen in tertiary syphilis, SLE, and DM: accommodation to near objects is intact, but the pupil does not react to light.

MNEMONIC

Argyll Robertson pupil is seen in the 3 Ss: Syphillis, SLE, and Sugar (DM).

KEY FACT

Marcus Gunn pupil results from a deficit in the afferent light reflex pathway (CN II palsy, retinal detachment). The affected pupil appears to expand when consensual light is removed from the unaffected eye → pupil is actually returning to baseline from a constricted state. Diagnose by swinging a light from pupil to pupil; usually seen in the context of MS.

KEY FACT

Xenophthalmia (dry eyes) may be caused by vitamin A deficiency (desquamation of conjunctival cells) or Sjögren's syndrome (keratoconjunctivitis sicca).

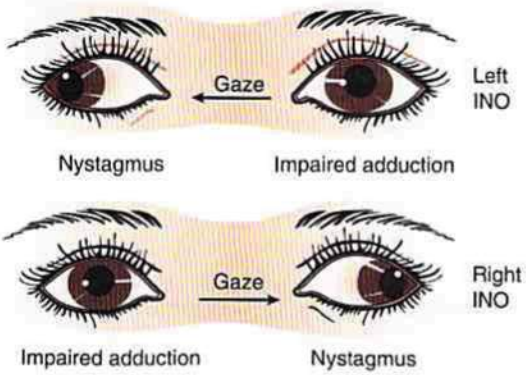


FIGURE 6-67. A clinical exam for MLF syndrome. When looking left, the left nucleus of CN VI fires, which contracts the left lateral rectus and stimulates the contralateral nucleus of CN III via the right MFL to contract the right medial rectus.

KEY FACT

Macular degeneration occurs secondary to disruption of the retinal membrane, leading to slow-onset loss of central vision with preserved peripheral vision. Most common cause of premature vision loss in the elderly.

KEY FACT

Cataracts (opacity of lens) are seen in the elderly and in those with DM, rubella, and corticosteroid use.

KEY FACT

Lens dislocation is seen in homocystinuria (inferior), Marfan's syndrome (superior), and Alport's syndrome (glomerulonephritis with blindness and deafness).

KEY FACT

Optic neuritis (inflammation of CN II) results in loss of vision and Marcus Gunn pupil. Causes include MS and methyl alcohol poisoning.

PRESENTATION

When the affected eye is adducting, nystagmus is seen in the abducting opposite eye (see Figure 6-67). Normal convergence ("finger to nose" eye test), but loss of conjugate gaze (see Figure 6-68). In patients with MS, results from demyelination of the MLF.

DIAGNOSIS

Clinical; if bilateral, high suspicion that MS is the etiology. Need to exclude myasthenia gravis in patients with isolated medial rectus palsy.

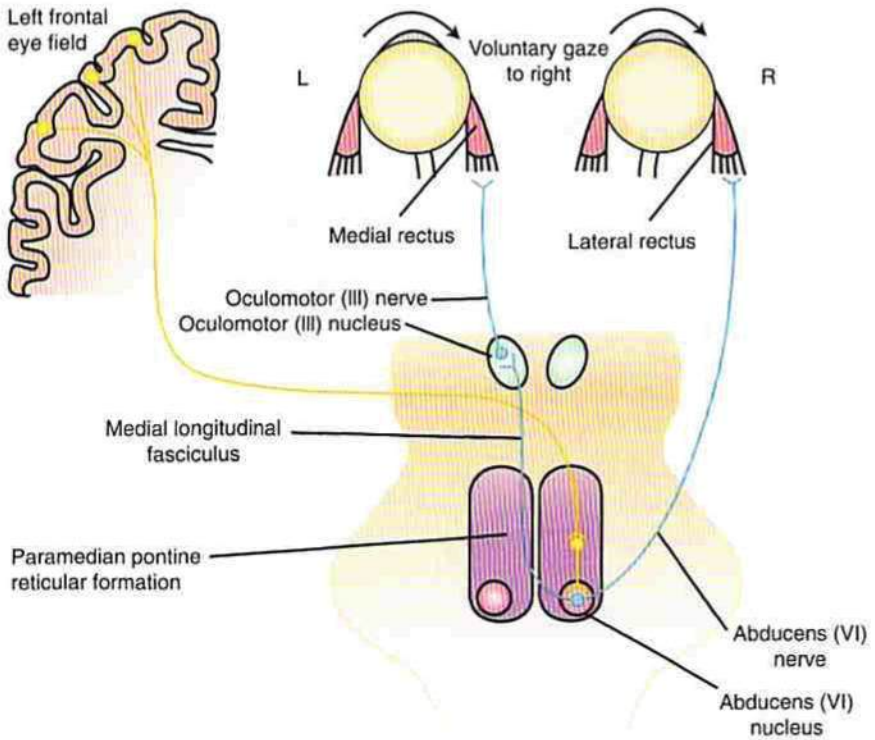


FIGURE 6-68. Schematic illustrating pathway for conjugate horizontal gaze. (Modified, with permission, from Aminoff MJ, Greeberg DA, Simon RP. *Clinical Neurology*, 6th ed, New York: McGraw-Hill, 2005: 130.)

TREATMENT

Underlying condition needs to be managed for resolution of MLF syndrome.

CENTRAL NERVOUS SYSTEM INFECTIONS

Infections that arise in the CNS can be divided into those that affect immune-competent individuals and those that affect immune-compromised patients, with some specific exceptions. AIDS-defining lesions (fungal, JC viral infection, and *Mycobacterium tuberculosis*) typically occur in immune-compromised patients. Table 6-38 details the types of patients affected and the typical disease course.

Meningitis

Inflammation of the pia mater covering the brain may be bacterial, viral, or fungal. Usually occurs secondary to hematogenous spread.

KEY FACT

Amaurosis fugax is a sudden unilateral loss of vision due to embolization of retinal atheromatous plaque material to the ophthalmic artery. Associated with carotid bruit and atherosclerosis. Classic visual sign of TIA ("ischemia of the eye") that presents like a shade being pulled over the eye.

TABLE 6-38. CNS Infections According to Type of Microbe

TYPE	PRESENTATION	CAUSATIVE MICROBE
Viral	Acute	Echovirus is most common cause of aseptic meningitis.
	Slow onset	Herpes encephalitis.
		CJD (prions); PML (JC virus), SSP rubeola (measles).
Bacterial	1-m-old	Group B streptococci, *Escherichia coli, Listeria monocytogenes.*
	1 m to 18 y	*Neisseria meningitidis* (*Haemophilus influenzae* is now rare because of vaccine).
	> 18 y	*Streptococcus pneumoniae.*
	Immunocompromised	*Mycobacterium tuberculosis* (complication of primary TB).
	Liver/renal disease, aseptic meningitis (Weil's syndrome)	Leptospirosis.
Fungal	Immunocompromised (subacute meningitis)	*Cryptococcus neoformans.*
	DKA, leukemia	Mucormycosis.
Parasitic	Rapidly fatal	*Naegleria fowleri.*
	Neurocysticercosis	*Taenia solium.*
	AIDS	*Toxoplasma gondii.*
	Malaria with CNS infection	*Plasmodium falciparum.*
Brain abscess	Bacterial	Streptococci, *Staphylococcus aureus*, Enterobacteriaceae, *Bacillus fragilis*, peptostreptococci.
	Helminthic	*Taenia solium*, schistosomiasis, hydatid cyst (*Echinococcus granulosus*).

KEY FACT

Glaucoma develops as a result of increased intraocular pressure that leads to optic atrophy. Increased intraocular pressure may be a consequence of decreased flow of aqueous humor through the canal of Schlemm or narrowing of the anterior chamber angle.

FLASH FORWARD

Nystagmus and acute altered mental status are pathognomonic for PCP intoxication. It is also seen in alcohol intoxication.

PRESENTATION

Nuchal rigidity, fever, meningismus (pain on flexion or extension of the neck), Kernig's sign (supine with hip and knee flexion to 90°; inability to extend the knee), Brudzinski's sign (supine flexion of the neck causes hip and knee flexion).

DIAGNOSIS

History and physical exam; lumbar puncture reveals signature CSF.

TREATMENT

Antibiotics and corticosteroids to avoid scarring.

PROGNOSIS

With an intact immune system and rapid diagnosis, good prognosis. May develop cerebral edema, SIADH, hydrocephalus, or subdural empyema (bacterial meningitis).

HERNIATION SYNDROMES

Portions of the brain under increased pressure are displaced through openings of dura partitions or into openings of the skull (e.g., foramen magnum) (see Figure 6-69). Therefore, treatment is aimed at removing the insult that generated the increased pressure (shunt for hydrocephalus, control of intracranial hemorrhage). Treatment with dexamethasone will mitigate cerebral edema and thereby reduce ICP. If the herniation affects the midline of the cortex, the patient will present with incontinence.

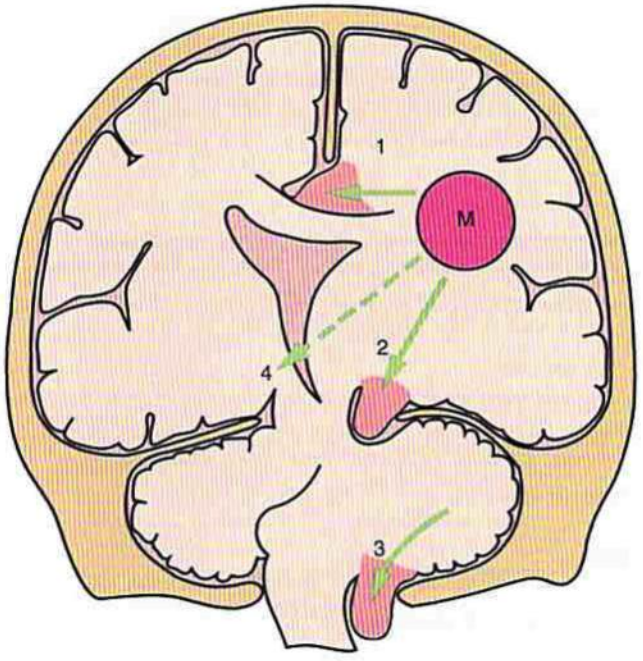


FIGURE 6-69. Way in which mass effect may result in any of the four types of herniation syndromes. Types Include (1) transtentorial, (2) uncal, (3) cerebellar tonsilar, and (4) cingulate. (Modified, with permission, from Ropper AH, Brown RH. *Adams and Victor's Neurology*, 8th ed, New York: McGraw-Hill, 2005: 310.)

Transtentorial

Coma and death result when these herniations compress the brain stem.

Uncal

Definition and Epidemiology

The medial temporal lobe compresses the crus cerebri by herniating through the tentorium cerebri. Results from a subdural or epidural hematoma that forces the medial aspect of the temporal lobe under the tentorium cerebri.

Presentation

- Stretching CN III leads to ipsilateral dilated pupil, ptosis (first loss of papillary light reflex, then loss of motor function).
- Compression of the ipsilateral posterior cerebral artery leads to contralateral homonymous hemianopia secondary to hemorrhagic infarct of the occipital lobe.
- Compression of the ipsilateral crus cerebri (lateral CST) leads to contralateral paresis.
- Compression of the contralateral crus cerebri (lateral CST, Kernohan's notch) leads to ipsilateral paresis.
- Caudal displacement of the brain stem (compression of the midbrain) leads to Duret hemorrhages, paramedian artery rupture, and midbrain hemorrhage.

Cerebellar Tonsillar

Herniation of the cerebellar tonsil into the foramen magnum results in cardiorespiratory arrest by compression of the medulla.

Cingulate

Under the falx cerebri, cingulate herniation may compress the anterior cerebral artery, leading to symptoms detailed earlier in the cerebrovascular section. The falx cerebri normally separates the two cerebral hemispheres along the midline of the skull.

Pharmacology

OVERVIEW

CNS pharmacology is a vast and complicated field. From the use of ether and chloroform in surgery in the 1840s to the purification of barbiturates at the turn of the 20th century, nervous system medications have defined many aspects of modern medicine. Although these drugs have been heavily studied, much remains unknown. Yet, understanding their properties has become a useful tool in the understanding of CNS physiology as well as the pathophysiology of common diseases.

CENTRAL NERVOUS SYSTEM NEUROTRANSMITTERS

An increase or decrease of certain neurotransmitters and/or their receptors has been implicated in many neurologic disorders. Certain therapies therefore target neurotransmitters or their receptors. There are multiple subtypes of dopamine, serotonin, and noradrenegic receptors throughout the CNS and the human body. Because no two medications in a class of drugs (e.g., antide-

pressants, atypical antipsychotics) have the same action on the same combination of receptors, there are differences in the clinical effect and side effects in patients. A very basic example of a synaptic neurotransmission site is shown in Figure 6-70.

KEY FACT

The **nucleus basalis of Meynert** is an important site for the production of Ach in the brain.

Acetylcholine

A neurotransmitter of both the PNS and CNS, this molecule has two classes of receptors: nicotinic and muscarinic. It is formed in the nerve terminal by choline acetyltransferase (see Figure 6-71). Ach is implicated in Alzheimer's dementia (decreased levels). Like histamine receptors, muscarinic Ach receptors can be blocked by **antipsychotics** and **tricyclic antidepressants**, resulting in dry mouth, blurred vision, and urinary hesitancy.

KEY FACT

The **substantia nigra pars compact** and the **ventral tegmental area** are important sites for the synthesis and use of dopamine in the brain.

Dopamine

A neurotransmitter synthesized from tyrosine that serves as a precursor to norepinephrine (NE); (see Figure 6-72), dopamine is implicated in psychosis (increased levels), mania (increased levels), schizophrenia (increased levels), and Parkinson's disease (decreased levels).

γ-Aminobutyric Acid (GABA)

The major inhibitory neurotransmitter in the CNS, GABA is associated with anxiety (decreased levels) and epilepsy (decreased levels). Anxiolytics (benzodiazepine and barbiturates) target the $GABA_A$ receptor (see anxiolytics and hypnotics for further explanation of benzodiazepines and barbiturates).

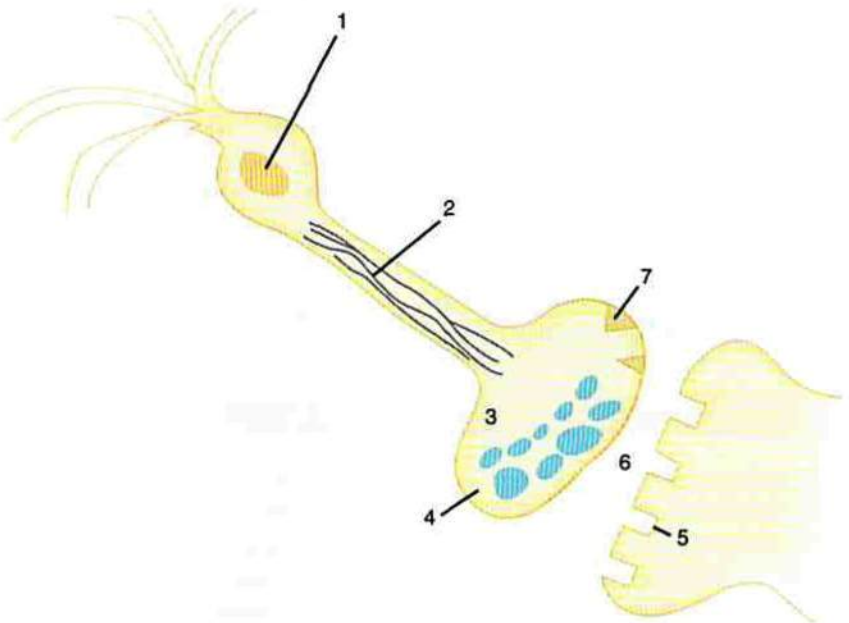


FIGURE 6-70. Synaptic neurotransmission site. (1) Cell body. (2) Microtubules. (3) Site of precursor or neurotransmitter uptake for presynaptic storage vesicles. (4) Presynaptic storage vesicles. (5) Postsynaptic neurotransmitter receptors. (6) Reuptake of the released neurotransmitter back into the presynaptic vesicle. (7) Presynaptic neurotransmitter receptors. (Modified, with permission, from Ebert MH, Loosen PT, Nurcombe B. *Current Diagnosis & Treatment in Psychiatry*. New York: McGraw-Hill, 2000: 30.)

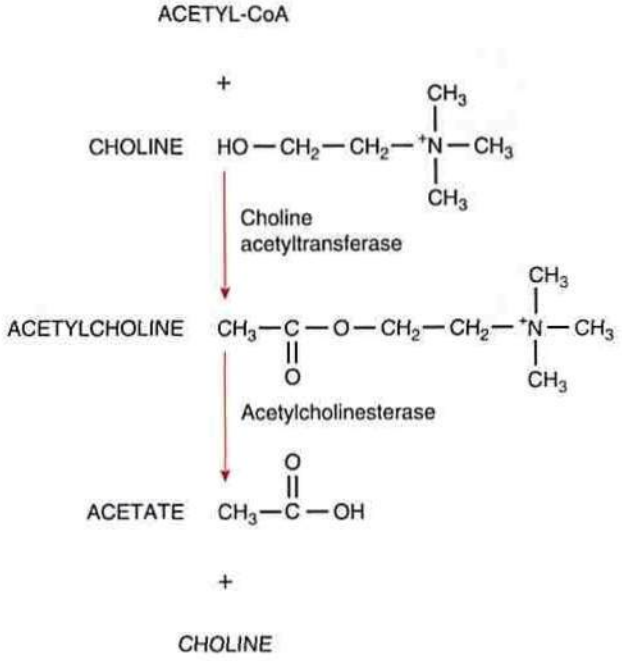


FIGURE 6-71. Synthesis and degradation of acetylcholine. Acetyl-CoA and choline combine with help from the enzyme choline acetyltransferase to form acetylcholine. Acetylcholinesterase is responsible for breaking down the neurotransmitter into acetate and choline.

Glutamate

The major excitatory neurotransmitter in the CNS, glutamate is implicated in epilepsy (increased levels), schizophrenia (increased levels), and Alzheimer's disease (increased levels).

Glycine

Glycine is an inhibitory neurotransmitter that controls/modulates glutamate activity in the brain.

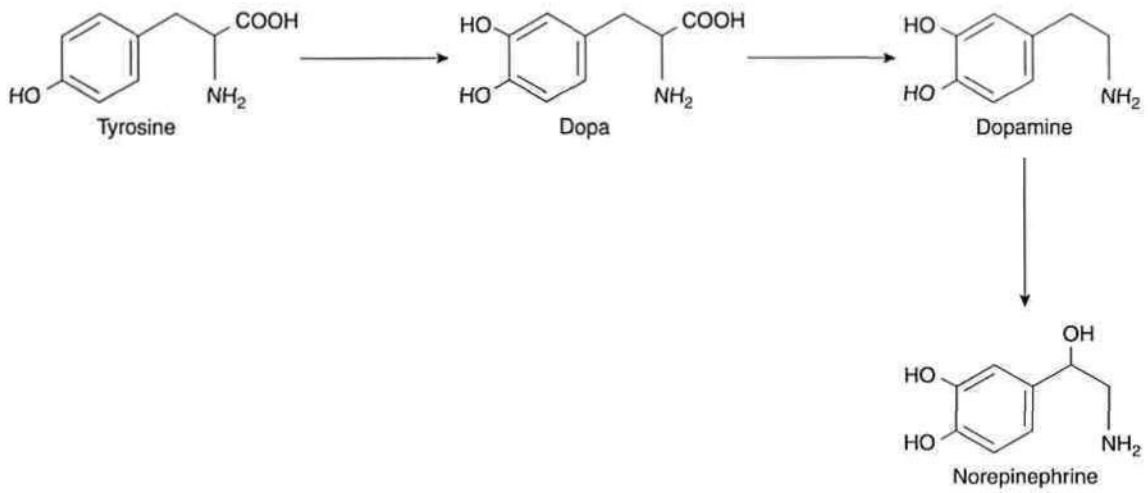


FIGURE 6-72. Synthesis of dopamine and norepinephrine. Dopa, dopamine, and norepinephrine are all derivatives of the amino acid tyrosine. (Modified, with permission, from Ebert MH, Loosen PT, Nurcombe B. *Current Diagnosis & Treatment in Psychiatry.*, New York: McGraw-Hill, 2000: 31.)

KEY FACT

Histaminergic neurons are located in the **ventral posterior hypothalamus.**

KEY FACT

The **locus ceruleus,** found in the upper pons, is the site of the majority of the NE in the brain.

Histamine

A ubiquitous chemical that, in the CNS, is responsible for sleep modulation and satiety. Antipsychotics and tricyclic antidepressants can cause histamine (H1)-receptor blockade, leading to side effects such as sedation and increased appetite, leading to weight gain.

Norepinephrine

A catecholamine precursor to epinephrine found at sympathetic postganglionic terminals (see Figure 6-72). It is implicated in major depressive disorder (decreased) and anxiety (increased).

Serotonin (5-Hydroxytryptamine)

A monoamine neurotransmitter that regulates mood, body temperature, sexuality, and sleep. It is converted from tryptophan in a series of reactions (see Figure 6-73) and is degraded by the enzyme monoamine oxidase. It is impli-

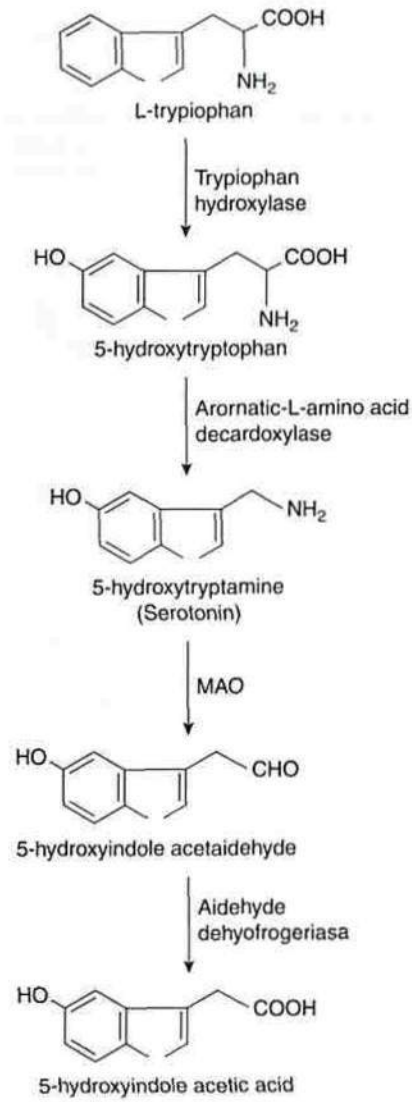


FIGURE 6-73. Synthesis of serotonin. Serotonin is a derivative of the amino acid tryptophan and is converted by monoamine oxidase to yield 5-hydroxyindole acetaldehyde. (Modified, with permission, from Ebert MH, Loosen PT, Nurcombe B. *Current Diagnosis & Treatment in Psychiatry*. New York: McGraw-Hill, 2000: 34.)

cated in major depressive disorder (decreased), bipolar disorder (decreased), anxiety disorder (decreased), and schizophrenia (increased).

KEY FACT

The **raphe nucleus** in the brain stem releases serotonin to projections throughout the brain.

AUTONOMIC DRUGS

Autonomic drugs are chemical agents that act within the autonomic nervous system at sympathetic and parasympathetic nerve terminals (see Figure 6-74). These drugs interact with preexisting neurotransmitters in order to achieve desired effects at the junction of the CNS and the PNS.

Neuromuscular Junction Blocking Agents

NMJ blocking agents are drugs used for skeletal muscle relaxation. These agents work at the NMJ, as opposed to inhaled anesthetics or regional nerve blocks, which act at different sites (see Figure 6-53). Because they work only at the NMJ, these agents do not cause analgesia or unconsciousness, **only paralysis.** They are similar in structure to Ach, allowing them to bind to Ach receptors on the muscle membrane. The two classes of NMJ blocking agents work differently at the Ach receptor; **depolarizing** agents behave as Ach receptor **agonists**, and **nondepolarizing** agents behave as Ach receptor **competitive antagonists.**

Depolarizing Agents

Drug Name

Succinylcholine (short-acting).

Mechanism

In general, depolarizing agents, such as succinylcholine, work as Ach receptor agonists. They achieve their desired effect in two distinct phases. In phase I, the drug binds aggressively to the Ach receptor and triggers depolarization

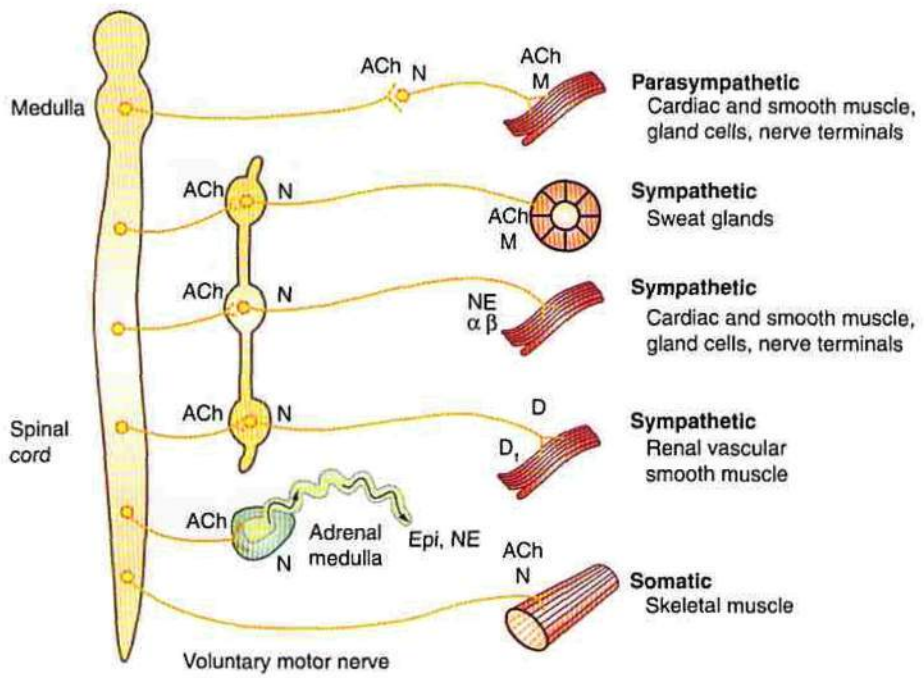


FIGURE 6-74. The autonomic nervous system. (Modified, with permission, from Katzung BG. *Basic & Clinical Pharmacology*, 10th ed, New York: McGraw-Hill, 2007: 76.)

of the motor endplate. However, it is resistant to AchE and remains bound to the Ach receptor. Sodium channels found at the motor endplate that initially closed after depolarization remain closed since the drug remains bound to the receptor and prevents repolarization of the motor endplate. Phase II occurs after the drug remains bound to the Ach receptor over time and induces a conformational change at the NMJ. Succinylcholine works within 30 seconds and lasts for 10 minutes. **Pseudocholinesterase** metabolizes succinylcholine before the drug reaches the site of action. Little of the drug is required to achieve the desired effects; the drug eventually diffuses away from the NMJ over 10 minutes.

Uses

Succinylcholine is the only clinical depolarizing agent used in the United States. It is used to cause muscle paralysis (e.g., surgery, intubation).

Side Effects

- Cardiovascular.
  - Low dose: Negative chronotropic and inotropic effects.
  - High dose: Positive chronotropic and inotropic effects; raises catecholamine levels.
- Fasciculations.
- Myalgia (visible motor unit contractions).
- Hyperkalemia (can raise serum potassium levels by 0.5 mEq/L, which is a concern in burn/trauma injury, spinal cord injury, cardiac disease, or metabolic abnormalities).
- Malignant hyperthermia.

Nondepolarizing Agents

Drug Names

Mivacurium (short-acting), vecuronium (intermediate-acting), rocuronium (intermediate-acting), atracurium (intermediate-acting), pancuronium (long-acting), doxacurium (long-acting).

Mechanisms

Nondepolarizing agents work through Ach receptor competitive antagonists. The drug binds to the Ach receptor, but does not cause the motor endplate to depolarize. By binding to the receptor, it prevents Ach from binding and prevents depolarization of the motor endplate, causing paralysis. Most nondepolarizing agents depend on hepatic or renal elimination to terminate their effect. Mivacurium is metabolized by pseudocholinesterase. Reversal of nondepolarizing block depends on metabolism of the drug or administration of a reversal agent.

Uses

Nondepolarizing agents are similar to depolarizing agents in causing muscle paralysis and are used in lieu of depolarizing agents as a muscle relaxant. Such uses include intubation, prevention of fasciculations (especially important in patients who may be sensitive to variations in serum potassium levels), decreasing the amount of inhalational agents, and maintenance of paralysis.

Side Effects

- Respiratory failure due to diaphragmatic paralysis
- Tachycardia (pancuronium)
- Histamine release (mivacurium)

Cholinesterase Inhibitors

Drug Names

Neostigmine, pyridostigmine, edrophonium, physostigmine.

Mechanisms

These drugs act by causing electrostatic or covalent bonding to AchE molecules, causing inactivation. They are used to reverse a nondepolarizing neuromuscular drug. They prevent degradation of Ach at the NMJ and therefore increase the available Ach at the junction to compete for Ach receptors, causing the nondepolarizing agent to "wash out." Reversal agents are contraindicated in depolarizing agents because they inhibit cholinesterase and pseudocholinesterase and thus prolong the phase I block.

Uses

They are used to reverse nondepolarizing neuromuscular drugs (e.g., pancuronium) during surgery.

Side Effects

- Bradycardia
- Bronchospasm
- Excitation (physostigmine)
- Intestinal spasm
- Increased bladder tone
- Papillary constriction

Anticholinergic Drugs

Drug Names

Atropine, scopolamine, benztropine, glycopyrrolate.

Mechanisms

These drugs competitively block Ach receptors from Ach and therefore prevent the neurotransmitter from acting (similar to the way nondepolarizing neuromuscular agents work at the NMJ) by binding to the Ach receptor and competitively blocking the site to prevent activation from Ach.

Uses

These drugs are primarily used in anesthesiology. However, these drugs have many uses outside of anesthesiology, as they affect many organ systems.

- Glycopyrrolate is a charged molecule and will not cross the BBB to cause CNS effects.
- Scopolamine is generally administered for its CNS effects.
- Atropine is generally administered for it cardiovascular effects:
  - Reversing vagal-stimulated bradycardia.
  - Decreasing respiratory tract secretions.
  - Bronchial smooth muscle relaxation.
  - Reversal of antipsychotic extrapyramidal side effects.

Side Effects

- CNS stimulation
- Cutaneous blood vessel dilation
- Urinary retention
- Cycloplegia
- Decreased secretions



MNEMONIC

Adverse side effects of anticholinergic drugs: "blind as a bat, dry as a bone, red as a beet, mad as a hatter, and hot as a hare."

ANXIOLYTICS AND HYPNOTICS

Both benzodiazepines and barbiturates target $GABA_A$ receptors. Typically, activation of the $GABA_A$ receptor causes a chloride ion channel to open, allowing chloride to enter and hyperpolarize the cell. With both types of medications, there are concerns about tolerance (decreased responsiveness after repeated doses) and withdrawal (physical dependence with absence of medication).

Barbiturates

Drug Names

Phenobarbital, pentobarbital, thiopental, secobarbital.

Mechanisms

Barbiturates increase the duration of chloride channel opening on $GABA_A$ receptors, resulting in enhanced GABAergic transmission. Barbiturates can block excitatory glutamate receptors in addition to targeting GABA receptors. They also induce CYP-450 microsomal enzymes in the liver so that other drugs that are metabolized by this system are eliminated more quickly.

Phenobarbital is 75% inactivated in the liver and 25% excreted in the urine unchanged.

Uses

Barbiturates have many clinical uses. Certain short-acting agents (e.g., thiopental, methohexital) are used during anesthesia. Other agents, like phenobarbital, are used as an anticonvulsant in the long-term management of tonic-clonic seizures, status epilepticus, and eclampsia. Anxiolytic properties of barbiturates make them applicable for use as mild sedatives that relieve anxiety. Furthermore, clinicians can use barbiturates in the treatment of insomnia (barbiturates suppress REM sleep more than other stages of sleep).

Side Effects

- High risk of dependence.
- Synergistic effects with alcohol.
- Respiratory, cardiovascular, CNS depression enough to cause coma and death.
- Induction of cytochrome P-450.
- Contraindicated in patients with acute intermittent porphyria.

Treatment of overdose consists of managing symptoms (ABCs) and hemodialysis in severe cases. Alkalinization of urine can aid in the elimination of phenobarbital.

Withdrawal

Barbiturate withdrawal can mimic alcohol withdrawal. The withdrawal syndrome includes:

- Anxiety
- Irritability
- Elevated heart and respiration rate
- Muscle pain
- Nausea
- Tremors

- Hallucinations
- Confusion
- Seizures
- Death is possible if untreated

Barbiturate withdrawal syndrome is dangerous and must be treated in the hospital conservatively. Phenobarbital can be used to slowly detoxify the patient.

MNEMONIC

Barbi**DURAT**e increases the **DURAT**ion of opening of the $GABA_A$ receptor.

Benzodiazepines

Drug Names

Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam.

MNEMONIC

For short-acting benzodiazepines, think: **TOM** Thumb.
Triazolam
Oxazepam
Midazolam.

Mechanisms

Increased frequency of chloride channel opening associated with binding of the benzodiazepine on the $GABA_A$ receptor. The entry of chloride hyperpolarizes the cell, making it more difficult to depolarize; therefore, it reduces neural excitability. The effects of this class of drugs are terminated through both redistribution and excretion (metabolized by the hepatic microsomal system into active metabolites). Benzodiazepines can cross the placental barrier.

Uses

Benzodiazepines have a number of clinical uses. They can be used as anxiolytics (via inhibition of neuronal circuits in the limbic system), as muscle relaxants to treat muscle spasms, as amnesic agents for endoscopic procedures (e.g., upper endoscopy, colonoscopy), and as anticonvulsant agents.

KEY FACT

Benzodiazepines cause a decrease in the latency to sleep onset and increase stage 2 of non-REM sleep. Both REM sleep and slow-wave sleep are decreased,

Side Effects

- Synergistic effects with alcohol
- Respiratory depression and coma (much less than with barbiturates)
- Drowsiness and confusion
- Tolerance
- Dependence

It is possible to reverse the effects of a benzodiazepine with **flumazenil**, a competitive antagonist at the benzodiazepine receptor.

Withdrawal

Long-term use of benzodiazepines can lead to tolerance and dependence. Withdrawal is similar to barbiturate withdrawal, but rarely as severe. Signs of benzodiazepine withdrawal include:

- Confusion
- Anxiety
- Agitation
- Restlessness
- Insomnia
- Tension

MNEMONIC

Benzodiazepines should be called **FRE**nzodiazepines because they increase the **FRE**quency of chloride ion entry through the $GABA_A$ receptor.

Opioids

Drug Names

Morphine, hydromorphone, oxymorphone, methadone, meperidine, fentanyl, sufentanil, altentanil, remifentanyl, codeine, hydrocodone, oxycodone, buprenorphine.

Mechanisms

Opioids are analgesics that act on the CNS. Opioids are either endogenous (endorphins, met- and leu-enkephalins, and dynorphins) or exogenous (derived from opium or synthetically created). Endogenous endorphins are formulated from pro-opiomelanocortin (POMC), which is also responsible for the formation of adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), and lipotropin (LPH). Synthetic opioids are structurally similar to endogenous opioids, but have been altered to achieve distinct properties. In general, opiates act as agonists on the μ-opioid receptor, although various formulations have varying strengths (full agonist vs. partial or weak agonist). Opioids provide analgesia by binding μ-opioid receptors in the CNS. By activating these receptors, the ascending pain pathways are modulated,

Uses

Common uses of opioids include local analgesia (e.g., regional nerve blocks, epidural nerve blocks, spinal nerve blocks), systemic pain relief (e.g., patient-controlled analgesia), and chronic pain management (e.g., transdermal patches). They are also used in antitussives (e.g., liquid formulations). Opioids are frequently substances of abuse for IV drug abusers (heroin).

Side Effects

- Tolerance
- Dependency
- Overdose potential

Buspirone

Mechanism

Buspirone works by partially antagonizing serotonin 1A (HT-1A) receptors in the CNS. Because it does not affect GABAergic receptors or benzodiazepine receptors, it is does not interact with ethanol, nor does it have as profound sedating properties, dependency qualities, and associated euphoria as benzodiazepines and barbiturates.

Uses

Buspirone is used for cases of mild anxiety.

Side Effects

- May stimulate the locus ceruleus (causing increased anxiety).
- May not work in patients with a history of benzodiazepine use or severe anxiety.

ANTIDEPRESSANTS

Antidepressants target imbalances in endogenous serotonin, NE, or dopamine. Heterocyclic agents (HCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants modulate the effects of endogenous neurotransmitters. Extended treatment with antidepressants leads to downregulation of postsynaptic neurotransmitter receptors. There are multiple receptors; no two antidepressants have the same receptor profile.

Selective Serotonin Reuptake Inhibitors

Drug Names

Citalopram, fluoxetine, paroxetine, sertraline, fluvoxamine.

Mechanisms

SSRIs are the current first-line treatment for depressive and anxiety disorders. They work by preventing reuptake of serotonin in the neurotransmitter synapse, allowing for increased availability of serotonin. It can take 3–6 weeks to see a desired effect clinically. Mood is not elevated in nondepressed patients, and mania may be precipitated in patients with bipolar disorder. SSRIs can be used in pregnant patients and the elderly because they have few side effects.

KEY FACT

Discontinuation syndrome consists of dizziness, vertigo, nausea, fatigue, headaches, insomnia, shock-like sensations, paresthesias, visual disturbances, muscle pain, chills, irritability, agitation, and suicidal thoughts.

Uses

SSRIs are used in illnesses other than depressive disorders. They can be used in the specific treatment of panic disorder, generalized anxiety disorder, and obsessive-compulsive disorder. Also, they can be used in the treatment of social anxiety disorder, posttraumatic stress disorder, eating disorders (e.g., fluoxetine in bulimia), and trichotillomania. In addition, SSRIs have been shown to decrease poststroke depression and morbidity/mortality in poststroke patients, even in the absence of depression.

KEY FACT

The most common congenital anomaly associated with SSRI use is ventral septal defect.

Side Effects

- Diarrhea.
- Sexual dysfunction (decreased libido, erectile dysfunction, anorgasmia).
- Weight gain.
- Fatigue.
- Discontinuation syndrome (worse with short-acting medications).
- Birth defects (absolute risk is small with all SSRIs, but greatest risk is with paroxetine).

Monoamine Oxidase Inhibitors

Drug Names

Phenelzine, tranylcypromine, isocarboxazid.

Mechanism

Monoamine Oxidase-A (MAO-A) is an enzyme that breaks down NE (see Figure 6-73). Inhibiting this breakdown irreversibly increases the amount of available NE. MAO is also responsible for the breakdown of serotonin and tyramine (see side effects for potentially fatal interactions with certain foods).

Uses

MAOIs are used to treat depressive disorders, including atypical depression (presenting with psychotic or phobic features), anxiety, and hypochondriasis. MAOIs have been used less often since the introduction of SSRIs because of their dangerous interaction with foods containing tyramine (see adverse effects below).

Side Effects

- Use with tyramine causes potentially fatal side effects and the following symptoms:
  - Hypertensive crisis
  - Diaphoresis
  - Headache
  - Vomiting

KEY FACT

Tyramine-rich foods include:
- Cheese (pizza)
- Pepperoni
- Beer
- Wine
- Smoked or pickled meat
- Liver
- Spoiled foods

- Use with SSRIs causes serotonin syndrome, characterized clinically as:
  - Confusion
  - Hyperthermia
  - Myoclonus
  - Diaphoresis
  - Hyperreflexia

Tricyclic Antidepressants

Drug Names

Amitriptyline, imipramine, amoxapine, clomipramine, desipramine, doxepin, nortriptyline, protriptyline.

Mechanisms

Tricyclic antidepressants (TCAs) increase the synaptic concentration of serotonin and/or NE in the CNS. They achieve this effect by inhibition of their reuptake by the presynaptic neuronal membrane, resulting in the availability of more drug to bind to postsynaptic neuronal receptors.

Uses

Tricyclic antidepressants can be used to treat chronic pain, major depression, and anxiety disorders. Historically, TCAs have been used in children for the treatment of enuresis. However, due to the incidence of sudden death, it is not a first-line treatment.

Side Effects

- **Constipation**
- **Cardiac arrhythmias**
- **Coma** (overdose potential)
- Sudden death in children (imipramine and desipramine)
- Sedation
- Tremor
- Insomnia
- Orthostatic hypotension
- Psychosis
- Seizures
- Weight gain

Nontricyclic Heterocyclic Antidepressants

Drug Name

Bupropion.

Mechanism

Bupropion is a heterocyclic antidepressant that can be used for smoking cessation. Although the mechanism of bupropion is not fully understood, it is generally considered to work by inhibiting the reuptake of dopamine and NE, allowing for increased amounts of both neurotransmitters to bind to their respective receptors in the CNS. This allows the drug to be useful in patients in whom TCAs are not tolerated due to side effects (e.g., orthostatic hypotension). The mechanism for smoking cessation is also unknown, but it is believed to be mediated through a similar pathway.

Uses

Nontricyclic heterocyclic antidepressants are second- and third-line medications used in the treatment of major depression and smoking cessation. They are also used in patients who do not tolerate TCAs.

Side Effects

- Stimulant effects
- Tachycardia
- Insomnia
- Headaches
- Seizure risk is greater than with other antidepressant drugs

Contraindicated in the following conditions:

- Anorexia
- Bulimia
- Seizure disorders (lowers threshold)
- MAOI treatment within the past 2 weeks

Drug Names

Venlafaxine, duloxetine.

Mechanisms

Both venlafaxine (which is converted to an active metabolite O-desmethylvenlafaxine) and duloxetine work through a similar mechanism to achieve their antidepressant effects. Both medications work to inhibit the reuptake of serotonin and NE. The exact mechanism by which they inhibit reuptake is unknown. Both venlafaxine and duloxetine inhibit serotonin reuptake more than NE reuptake.



MNEMONIC

Both **VE**nlafaxine and **DUAL**oxetine are **VE**ry good **DUAL** inhibitors.

Uses

These serotonin and NE reuptake inhibitors are used to treat major depression, including melancholia (venlafaxine), anxiety disorders, chronic pain associated with depression, and diabetic peripheral neuropathic pain (duloxetine).

Side Effects

- Sedation
- Nausea
- Constipation
- Elevated BP
- Sweating
- SSRI discontinuation syndrome

Drug Names

Nefazodone, trazodone, mirtazapine.

Mechanisms

These medications are serotonin modulators. They block the 5-HT2 receptor and inhibit reuptake of 5-HT and NE. Mirtazapine also antagonizes histaminic H1 receptors and weakly blocks peripheral α1-adrenergic and muscarinic receptors. Trazodone can antagonize serotonin at low doses and behaves

like a serotonin agonist at high doses. In addition to blocking presynaptic serotonin reuptake, trazodone is thought to have histamine blockade, allowing it to be useful in the treatment of insomnia.

Uses

These medications are used to treat major depression and anxiety disorders. In addition, trazodone may be used to treat insomnia.

Side Effects

- Sedation (especially low-dose mirtazapine)
- Increased appetite
- Weight gain
- Dry mouth
- Hepatotoxicity (nefazodone)
- Priapism (trazodone)
- Visual trails (nefazodone)
- Postural hypotension

Drug Name

Maprotiline

Mechanisms

Maprotiline is a tetracycline antidepressant drug that selectively prevents the reuptake of NE. Maprotiline does so at the neuronal membrane and differs from tricyclic antidepressants and heterocyclic antidepressants in that it does not prevent the reuptake of serotonin.

Uses

Maprotiline is used in the treatment of major depression.

Side Effects

- Sedation
- Orthostatic hypotension

NEUROLEPTICS

Neuroleptics (classified as first- and second-generation antipsychotics) block dopamine-2 receptors (D2). These drugs are most effective against the positive symptoms of schizophrenia, such as hallucinations and delusions.

First-Generation Antipsychotics

Drug Names

Chlorpromazine and thioridazine (low potency), haloperidol, trifluoperazine, pimozide, perphenazine (high potency).

Mechanisms

First-generation antipsychotics work in the mesolimbic system through blocking the postsynaptic D2 receptors. The low-potency drugs (e.g., chlorpromazine, thioridazine) also have an affinity for muscarinic Ach receptors and histaminergic receptors (see side effects). High-potency drugs (e.g., haloperidol) have greater affinity for D2 receptors.

Uses

First-generation antipsychotic drugs are useful in the treatment of acute psychosis as well as in patients with bipolar disorder. Haloperidol can be used in Tourette's syndrome (to control tics) and Huntington's disease (to combat choreiform movements associated with advanced disease).

Side Effects

- Extrapyramidal signs (parkinsonism, akathisia, tremor).
- Movement disorders (tardive dyskinesia, dystonias).
- Sedation.
- Neuroleptic malignant syndrome.
- Anticholinergic side effects.
- Sudden death from prolongation of the QT interval, leading to torsades de pointes (thioridazine).
- Irreversible retinal pigmentation (thioridazine).
- Deposits in the lens and cornea (chlorpromazine).

KEY FACT

Blockade of muscarinic receptors causes:
- Facial flushing
- Dry mouth
- Urine retention
- Constipation

Blockade of histamine receptors causes:
- Weight gain
- Sedation
- Orthostatic hypotension
- Tremor
- Sexual dysfunction

Second-Generation Antipsychotics

Drug Names

Clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole.

Mechanisms

Atypical antipsychotics bind to the serotonergic, dopaminergic (with affinity to D2), and noradrenergic systems. Each medication has a different neuroreceptor profile, accounting for differences in therapeutic action and side effects. There are several advantages of atypical antipsychotics over typical antipsychotics. Second-generation antipsychotics are more effective with negative and chronic symptoms of schizophrenia. In addition, there is a reduced chance of tardive dyskinesia, neuroleptic malignant syndrome, and extrapyramidal signs.

Uses

These medications are used to treat schizophrenia, psychosis, and bipolar disorder, and for antidepressant augmentation (risperidone).

Side Effects

- Cardiotoxicity.
- Weight gain.
- Neuroleptic malignant syndrome.
- Extrapyramidal reactions (see above).
- Agranulocytosis (clozapine).
- Increased chance of seizures.
- Weight gain (clozapine, olanzapine).
- Insulin intolerance, leading to type 2 diabetes (this side effect from some of the second-generation agents may be unrelated to weight gain).
- Hyperlipidemia.
- ECG abnormalities (prolongation of QT and PR intervals may occur with ziprasidone).
- Increase in prolactin levels (gynecomastia, galactorrhea, and amenorrhea, seen especially with risperidone).

Ziprasidone and aripiprazole have fewer metabolic side effects than the other second-generation antipsychotics.

MOOD STABILIZERS AND ANTICONVULSANTS

Mood Stabilizers

Drug Name

Lithium.

Mechanisms

The exact mechanism of this mood stabilizer is unknown. However, it is believed that lithium interferes with monoamine synthesis, release, and reuptake.

Uses

Lithium is used in the treatment of bipolar disorder and to augment antidepressants in major depressive disorder. Lithium may take 2–3 weeks to start working, and because of its low therapeutic index, its blood level must be followed and kept to the minimum therapeutic level. Creatinine and TSH must also be followed regularly.

Side Effects

- Hypothyroidism, goiter.
- Thirst.
- Tremor.
- Diarrhea.
- Renal dysfunction (nephrogenic diabetes insipidus, increased creatinine, eventual kidney failure).
- Increased appetite and weight gain.
- Cardiac conduction problems.
- Mild cognitive impairment.
- CNS depression and renal damage (at toxic levels).
- Congenital abnormalities.

Anticonvulsants

Anticonvulsants are agents that suppress uncontrolled neuronal discharge in epileptic seizures. Seizures are characterized as either partial or generalized, Within the partial seizures, a patient can have a simple seizure, a complex seizure, or a partial seizure with secondarily generalized tonic-clonic seizure. Of the generalized seizures, a patient can have an absence seizure, a myoclonic seizure, or a tonic-clonic seizure. Anticonvulsants work through three different types of mechanisms to reduce the likelihood that a seizure will occur. The mechanisms consist of inhibiting neuronal firing through GABA (presynaptic and postsynaptic mechanisms), through voltage-activated sodium channels, or through voltage-activated calcium channels (see Figures 6-75, 6-76, and 6-77, respectively).

Drug Name

Valproic acid.

Mechanism

Valproic acid or valproate (its dissociated or ionized form) works via binding to sodium channels and prolonging the inactivated state of the sodium channel (see Figure 6-76). It also has a role in decreasing calcium influx across the cell membrane, reducing the calcium current in certain neurons (see Figure 6-77), and may cause the release of various neurotransmitters (allowing it to be used in other disorders as well).

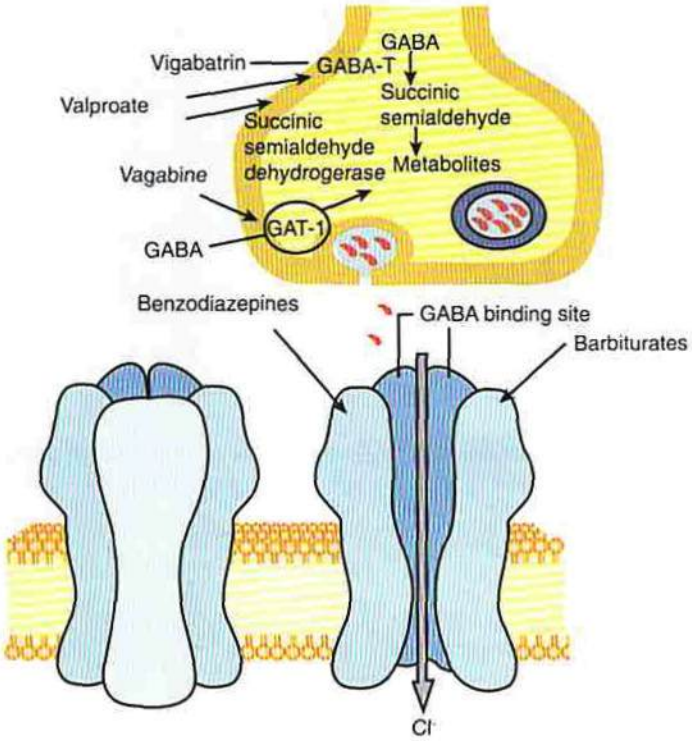


FIGURE 6-75. Anticonvulsants that target presynaptic and postsynaptic GABA and the GABA receptor. Vigavatrin, valproate, tiagabine, barbiturates, and benzodiazepines all target the role of GABA and its receptor in CNS inhibition. (Modified, with permission, from Katzung BG. *Basic & Clinical Pharmacology*, 10th ed. New York: McGraw-Hill, 2007: 506.)

Uses

Valproic acid is used for the treatment of partial and generalized tonic-clonic seizures, bipolar disorder, and intermittent explosive disorder. Also, it is used as prophylaxis for migraines. Use of this drug is decreasing due to the increased number of side effects and its lower efficacy compared with other medications.

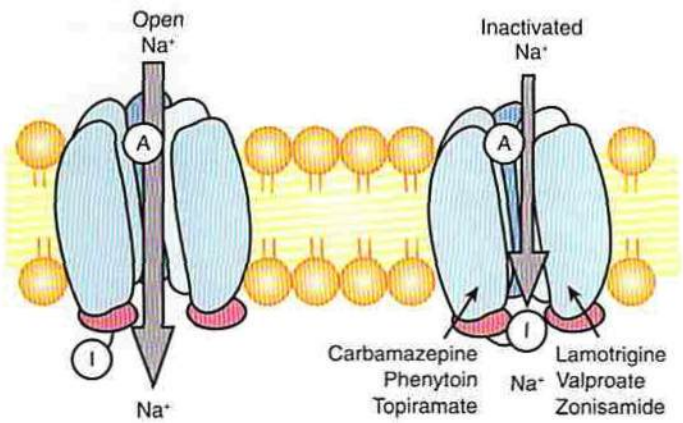


FIGURE 6-76. Anticonvulsants that target and extend sodium channel inactivation. Carbamazepine, phenytoin, topiramate, lamotrigine, valproate, and zonisamide all target sodium channels and aim to prolong their inactivation in the treatment of seizures. (Modified, with permission, from Katzung BG. *Basic & Clinical Pharmacology*, 10th ed. New York: McGraw-Hill, 2007: 505.)

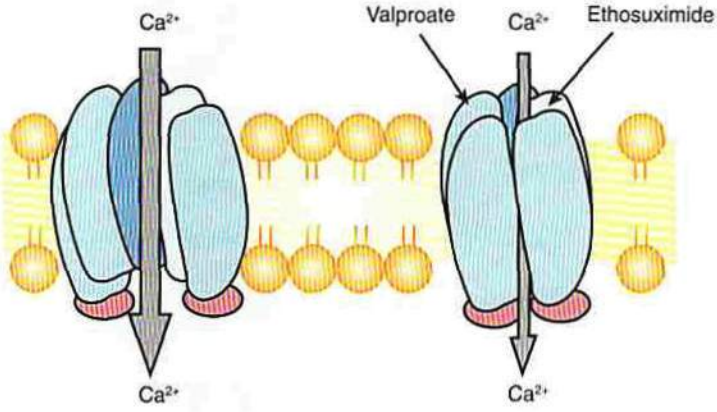


FIGURE 6-77. Anticonvulsants that target and reduce current through calcium channels. Only valproate and ethosuximide target and reduce current through T-type calcium channels in the treatment of generalized absence seizures.

Side Effects

- GI upset, with stomach pain, nausea, and diarrhea
- Increased appetite, leading to weight gain
- Tremor
- Sedation
- Alopecia
- Hepatotoxicity
- Decreased platelet count
- Possible polycystic ovarian syndrome
- Congenital neural tube defects

Drug Name

Ethosuximide.

Mechanisms

Ethosuximide, like valproic acid, works by reducing the calcium current in thalamic neurons. The thalamus is responsible for the generation of the 3-Hz spike-and-wave rhythms seen in absence seizures. By reducing these T-type currents in the neurons of the thalamus, ethosuximide can stop the rhythmic discharge associated with an absence seizure (see Figure 6-76).

Uses

Ethosuximide is typically used to treat absence seizures. Because it works in the thalamus, it has target-specific therapy.

MNEMONIC

e**TH**osuximide targets the **TH**alamus.

Side Effects

- GI distress
- Lethargy
- Headache
- Urticaria
- Stevens-Johnson syndrome

Drug Name

Phenobarbital.

Mechanisms

The barbiturate phenobarbital acts on the $GABA_A$ receptor. By doing so, it can increase CNS inhibition and raise the seizure threshold (see Figure 6-75).

Uses

Phenobarbital has many uses; however, its role in anticonvulsive therapy is specific to treating patients in status epilepticus.

Side Effects

- Sedation
- Tolerance
- Dependence
- Induction of cytochrome P-450 system

Drug Name

Carbamazepine.

Mechanisms

Carbamazepine works by reducing the rate of recovery of voltage-activated sodium channels, blocking the repeat firing of APs that is classically associated with partial seizures and generalized tonic-clonic seizures (see Figure 6-76).

Uses

Carbamazepine is used to treat partial seizures and tonic-clonic seizures as well as bipolar disorder and trigeminal neuralgia.

Side Effects

- Aplastic anemia.
- Agranulocytosis.
- Induces cytochrome P-450 enzymes, causing increased metabolism of many drugs, including itself and oral contraceptives.

Drug Name

Phenytoin.

Mechanisms

Like carbamazepine, it acts by slowing the rate of recovery of voltage-activated sodium channels (see Figure 6-76).

Uses

Phenytoin is used to treat all types of partial and tonic-clonic seizures (not absence seizures).

Side Effects

Toxicity (at high levels):

- Nystagmus
- Diplopia
- Ataxia
- Sedation
- Gingival hyperplasia
- Megaloblastic anemia
- SLE-like syndrome
- Induction of cytochrome P-450

Drug Name

Lamotrigine.

Mechanisms

Lamotrigine has a mechanism similar to that of phenytoin and carbamazepine (see Figure 6-76). In addition to these properties of prolonging inactivation of voltage-activated sodium channels, it may be associated with reducing the amount of released glutamate.

Uses

It is used to treat partial seizures, generalized tonic-clonic seizures, focal epilepsy, Lennox-Gastaut syndrome, and bipolar disorder.

Side Effects

- Dizziness
- Nausea
- Headache
- Skin rash (hypersensitivity reaction)
- Stevens-Johnson syndrome (avoided by increasing the dose very slowly)

Drug Name

Gabapentin.

Mechanisms

The mechanism of gabapentin is unknown, although it is thought to promote the release of GABA (see Figure 6-75).

Uses

Since it is a highly lipid-soluble drug, gabapentin is used in sedation as well as to treat partial seizures, pain, and anxiety.

Side Effects

- Sedation
- Weight gain

Drug Name

Pregabalin.

Mechanisms

The mechanism of action of pregabalin is unknown. Its antinociceptive and antiseizure effects may be due to binding to the α_2-δ subunit and modulation of calcium channel function. Pregabalin increases the density of the GABA transporter protein and increases the rate of functional GABA transport.

Uses

Pregabalin is used to treat neuropathic pain associated with diabetic neuropathy and postherpetic neuralgia and in the adjunctive treatment of partial-onset seizures and fibromyalgia.

Side Effects

- Dizziness
- Somnolence
- Weight gain

TREATMENTS FOR NEURODEGENERATIVE DISEASE

Drugs Used to Treat Alzheimer's Disease

The decrease in ACh levels and the increase in the excitatory neurotransmitter glutamate are a notable part of Alzheimer's disease. One strategy to prevent progression of Alzheimer's disease is by blocking the N-methyl-D-aspartate (NMDA) receptors that are activated by excess of glutamate. Likewise, since AChE breaks down ACh into choline and acetate (see Figure 6-71), blocking the action of AChE may aid in stopping disease progression and improving cognition.

N-Methyl-D-Aspartate: Glutamate Receptor Antagonist

Drug Name

Memantine.

Mechanism

During depolarization of neuronal cells, calcium bypasses the magnesium blockade on the NMDA receptor and enters the cell. Over time, the influx of calcium leads to neuronal damage. Memantine produces a noncompetitive blockade of NMDA receptors in the CNS. Once memantine has acted, the NMDA receptor cannot be stimulated by glutamate. This results in less intracellular calcium. In essence, lowering intracellular calcium levels spares the nerve from further damage.

Uses

Memantine is used to treat moderate to severe Alzheimer's disease. It may also have a role in the treatment of vascular dementia.

Side Effects

- Agitation
- Urinary incontinence
- Insomnia
- Diarrhea

Drug Names

Tacrine, donepezil, rivastigmine, galantamine.

Mechanisms

All of these medications are selective inhibitors of AchE in the CNS. By selectively inhibiting AchE in the CNS, levels of Ach will increase, with the goal of improving cognition. The benefits of having centrally acting AchE inhibitors are improved efficacy and decreased side effects (decreasing peripheral acetylcholinesterase and the associated peripheral side effects).

Uses

These drugs are generally used in the treatment of Alzheimer's disease because they are centrally acting. AchE inhibitors, in general, have multiple uses in medicine.

Side Effects

- Nausea
- Vomiting
- Diarrhea
- Insomnia

Drugs Used to Treat Parkinson's Disease

Parkinson's disease is caused by a loss of dopaminergic neurons (particularly D2 receptors). The death of these neurons, located in the substantia nigra pars compacta, results in lower levels of dopamine in the CNS. A lack of dopamine appears clinically with symptoms of mask-like facies, bradykinesia, resting tremor, muscle rigidity, and postural instability. Several strategies are used to increase the levels of endogenous dopamine by preventing its degradation, add exogenous dopamine that is converted centrally, or give dopamine agonists that directly stimulate D2 receptors (see Figure 6-78).

Drug Names

Bromocriptine, pergolide, ropinirole, pramipexole.

Mechanisms

Broadly, these drugs work as dopamine receptor agonists. However, each drug has different effects on the different types of dopamine receptors. For example,

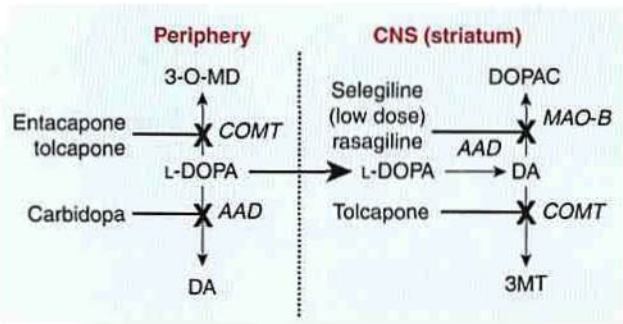


FIGURE 6-78. Relationship between peripheral and centrally acting drugs used to treat Parkinson's disease. (Modified, with permission, from Brunton LL, Lazo JS, Parker KL. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 11th ed, New York: McGraw-Hill, 2006: 536.)

pergolide is an agonist of both D1 and D2 receptors, ropinirole and pramipexole act only at D2 receptors, and bromocriptine is a D2 receptor agonist and D1 receptor antagonist. Bromocriptine also has properties that allow it to antagonize dopamine type 1 receptors in the hypothalamus.

Uses

These medications are used to treat Parkinson's disease. Bromocriptine can be used to reduce the rate of growth of pituitary adenomas and to treat acromegaly.

Side Effects

- Headache
- Nausea
- Vomiting
- Epigastric pain
- Hypotension/syncope initially, leading to hypertension over time

Drug Name

Levodopa.

Mechanisms

Levodopa is a metabolic precursor of dopamine that enters the brain through an L-amino acid transporter. Once there, it is further decarboxylated to dopamine. Levodopa appears in the urine as the metabolites homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC).

Uses

First-line medication in the treatment of Parkinson's disease.

Side Effects

- Nausea and vomiting
- Tachycardia
- Atrial fibrillation
- Dyskinesias
- Depression
- Agitation
- Confusion

Levodopa is contraindicated in psychosis and closed-angle glaucoma.

Monoamine Oxidase Inhibitors

Two types of monoamine oxidase have been distinguished in the nervous system:

- Monoamine oxidase A metabolizes NE and serotonin.
- Monoamine oxidase B metabolizes dopamine.

Drug Names

Selegiline, rasagiline.

Mechanisms

Selegiline is an irreversible selective inhibitor of MAO-B. MAO-B is found in the striatum and metabolizes dopamine in the brain.

Uses

Parkinson's disease; a skin patch is used in major depression.

Side Effects

- Serotonin syndrome (can occur when taken in combination with meperidine, TCAs, or SSRIs).

A selegiline preparation (EMSAM) is available in a skin patch that allows the drug to bypass the GI tract. Its low dose does not have the tyramine food interactions seen with other MAOIs.

Catechol-*O*-Methyltransferase Inhibitors

Drug Names

Tolcapone (central and peripheral), entacapone (peripheral).

Mechanisms

The catechol-O-methyltransferase inhibitors tolcapone and entacapone can prolong the action of levodopa by diminishing its peripheral and central metabolism. Entacapone is preferred to tolcapone (less hepatotoxicity).

Uses

Used to increase the levels of levodopa in the treatment of Parkinson's disease.

Side Effects

- Dyskinesias
- Nausea
- Confusion

CLINICAL ANESTHETICS AND ANALGESICS

General Anesthetics

General anesthetics are essential to surgery because they cause analgesia, amnesia, and unconsciousness. They also cause muscle relaxation and suppression of reflexes.

Stages of Anesthesia

Four sequential stages:

- Stage 1—Analgesia: "Conscious and conversational."
- Stage 2—Disinhibition: Autonomic variations (changes in BP, heart rate, and respiratory rate).
- Stage 3—Surgical anesthesia: Unconsciousness and muscle relaxation.
- Stage 4—Medullary depression: Respiratory and vasomotor center depression.

Method of Delivery

Inhaled agents are volatile, halogenated hydrocarbons that were derived from early research and clinical experience with ether and chloroform. IV drugs are typically used because of their common property of rapid induction.

Inhaled Anesthetics

Depth of anesthesia can be rapidly altered by changing the inhaled concentration of the drug, making it suitable for maintaining anesthesia. The speed of induction of inhaled anesthetics will depend on the alveolar gas and venous blood partial pressures, the solubility of the anesthetic agent in the blood, and the alveolar blood flow. The minimum alveolar concentration (MAC), which is very similar to ED_{50}, is equal to the alveolar concentration of an inhaled anesthetic that stops movement in 50% of patients in response to incision.

In order to cross the selectively permeable BBB, drugs must penetrate through lipids (lipophilic) or must be actively transported at the junction.

KEY FACT

Drugs with **low** solubility in blood have rapid induction and recovery times. Drugs with **high** solubility in lipids have increased potency.

Drug Names

Halothane, isoflurane, sevoflurane, desflurane.

Mechanisms

The mechanism of inhaled anesthetics is poorly understood.

Uses

Inhaled anesthetics are used in the maintenance of anesthesia.

Side Effects

- Respiratory depression
- Nausea
- Emesis
- Hypotension

Toxicity

- Hepatotoxicity (halothane)
- Nephrotoxicity (methoxyflurane; no longer used in the United States)
- Convulsions (enflurane)
- Malignant hyperthermia (all agents except nitrous oxide)

KEY FACT

Dantrolene is used to correct malignant hyperthermia because it interferes with calcium in the sarcoplasmic reticulum of muscle cells.

Intravenous Anesthetics

Used to rapidly induce anesthesia, with propofol having the ability to both induce and maintain anesthesia.

Types

- Barbiturates
- Benzodiazepines
- Ketamine
- Opiates
- Propofol

Barbiturates (Thiopental)

Highly lipid-soluble agents that enter the brain rapidly, making them suitable for induction of anesthesia and short surgical procedures. Redistribution from the brain causes loss of effects. They are not analgesic and therefore require a supplementary analgesic. IV barbiturates can cause severe hypotension in patients who are hypovolemic or in shock.

KEY FACT

Anesthetic concentrations of pentobarbital block high-frequency sodium channels.

KEY FACT

Opioids are reversed with naloxone, which antagonizes the opioid receptor.

MNEMONIC

B.B. King on **OPIATES PROPO**ses **FOOL**ishly.
Barbiturates
Benzodiazepines
Ketamine
Opiates
PROPOFOL

Benzodiazepines (Midazolam)

Most common drug used for endoscopy; it is used with inhalational anesthetics and narcotics. Midazolam causes severe postoperative respiratory depression and amnesia.

Ketamine (Arylcyclohexylamine)

A PCP analog that acts as a dissociative anesthetic (very high affinity for NMDA receptors). It causes sedation, amnesia, immobility, disorientation, and hallucinations.

Opioids (Morphine, Fentanyl, Sufentanil)

Used with other CNS depressants during general anesthesia. Toxicity causes hypotension, respiratory depression, and muscle rigidity.

Propofol

Used for rapid anesthesia induction and short procedures. An excitatory phase may occur, causing muscle twitching, spontaneous movements, and hiccups. It also can reduce ICP. Propofol is used in the resection of spinal tumors. Since it has much less effect than the volatile anesthetics on CNS-evoked potentials, it can be used to assess spinal cord function.

Rapid Review

Key Terms

Agnosia	Inability to identify an object by name despite the ability to describe the object.
Aphasia	Loss of ability to use or understand written or spoken language.
Athetosis	Writhing movements of the extremities that involve involuntary changes in posturing.
Broca's aphasia	Inability to form words and sentences due to an injury to Broca's area (comprehension is preserved).
Chorea	Involuntary movements of extremities or face that the patient may mask by turning them into "purposeful" movements.
Dysarthria	Difficulty pronouncing words.
Hemiballismus	Wild flailing of an arm due to injury to the subthalamic nucleus.
Wernicke's aphasia	Retains ability to form words and sentences but they are without coherence or meaning.

TABLE 6-39. Signs to Differentiate Upper and Lower Motor Neuron Lesions

SIGN	UMN	LMN
Weakness	+	+
Atrophy	–	+
Fasciculations	—	+
Reflexes	↑	↓
Tone	↑	↓
Babinski's sign	+	–

FINDINGS SUGGESTIVE OF INTRACRANIAL PATHOLOGY

Intracranial pathology will manifest clinically in a specific manner depending on the location of the lesion (upper motor neuron [UMN] versus lower motor neuron [LMN] involvement). Knowing the physical exam findings is useful in identifying the disease process (see Table 6-39).

NEURAL TUBE DEFECTS

The neural tube usually closes by the 28th day of gestation. Defects associated with abnormal closure are referred to as neural tube defects. They are associated with low folic acid intake during pregnancy, and elevated α-fetoprotein in amniotic fluid and maternal serum.

- **Anencephaly:** Severe neural tube defect with occurrence of 1 in 500 births. Folate deficiency and increased age of the mother are risk factors.
- **Encephaloceles:** Protrusion of a variable amount of meninges and brain parenchyma through a defect in the cranial bones (usually occipital).
- **Cranial meningoceles:** Distinguished from encephaloceles by the presence of only meninges and CSF in the herniated tissue.

Spina Bifida Occulta

Spina bifida occulta is a defect in posterior vertebral arch closure with intact meninges and spinal cord. The overlying skin may be dimpled,

Meningocele and Meningomyelocele

Meningomyelocele is herniation of spinal meninges and cord through a posterior vertebral defect to form a cyst-like outpouching (spina bifida cystica). If only the meninges herniate through the defect, it is termed meningocele.

- **Arnold-Chiari malformation:** Abnormally shallow posterior cranial fossa with caudal extension of the medulla oblongata and portions of the cerebellar vermis through the foramen magnum. Often seen with meningomyelocele and hydrocephalus.

- **Dandy-Walker malformation:** Characterized by aplasia/hypoplasia of the cerebellar vermis, dilation of the fourth ventricle, and enlarged posterior fossa. Usually associated with hydrocephalus.

DEGENERATIVE DISEASES

Degenerative diseases of the CNS present with some degree of cognitive impairment and dementia. May be associated with tremor or paralysis. These diseases usually affect the elderly.

Alzheimer's Disease (AD)

Most common cause of dementia (memory impairment and other cognitive deficits with preservation of a normal level of consciousness) in the elderly (most cases occur after age 50). Caused by a deficiency of acetylcholine from the nucleus of Meynert.

- **Amyloid precursor protein (APP):** Genetic mutation on chromosome 21 causes the production of APP. The breakdown of APP is the source of the β-amyloid deposits (which form the senile plaques) in the brains of patients with AD.
- **Tau protein:** Intracellular protein involved in the assembly of intra-axonal microtubules. Patients with AD have a hyperphosphorylated tau protein that accumulates, leading to cytoskeletal abnormalities (another feature of AD).
- **Apolipoprotein E:** Expressed with increased frequency in patients with late-onset AD. It may be involved with the transport and processing of APP.
- **Neurofibrillary tangle:** Microscopic changes in the brain, which appear as coarse, filamentous aggregates within the cytoplasm of neurons. They are composed of protein-rich paired helical filaments (PHFs), the main component of which is hyperphosphorylated tau protein.
- **Senile plaque:** Appear as aggregates of coarse, tortuous neurites in the neuropil of the cerebral cortex with a central amyloid core.
- **Amyloid angiopathy:** Deposition of β-amyloid in the meningeal and parenchymal vessels, as well as senile plaques.

Parkinsonism

Presents after the sixth decade. A progressive disturbance in motor function with insidious onset characterized by rigidity, expressionless facies, stooped posture, gait disturbances, slowing of voluntary movements, and a characteristic pill-rolling tremor. Involves the dopamine-secreting neurons of the substantia nigra and locus ceruleus.

- **Substantia nigra and locus ceruleus:** Two areas that become depigmented as a result of loss of melanin-containing neurons. The neuropil is gliotic, and some of the remaining neurons in these areas contain concentrically laminated eosinophilic, intracytoplasmic inclusions known as Lewy's bodies.

Huntington's Disease (HD)

Hereditary (autosomal dominant), progressive (over 15–20 years), fatal disorder involving the extrapyramidal motor system, characterized by involuntary,

writhing movements (chorea) and dementia. It usually presents between the fourth and fifth decades.

- **Trinucleotide repeat mutation:** CAG repeats affecting the huntingtin gene on chromosome 4 have been identified as the cause of HD. The result of this mutation is some degree of impairment of the normal protein produced by the huntingtin gene (gain-of-function mutation).

Amyotrophic Lateral Sclerosis (ALS)

Fatal degenerative disorder involving the upper and lower motor neurons of the pyramidal system, with resultant progressive muscle weakness, atrophy, and spasticity. As such, it presents with the slow onset of weakness progressing to atrophy and small involuntary muscle contractions (fasciculations). It exists in hereditary and sporadic forms, but the cause is unknown. Some suggest an SOD mutation.

- **Precentral gyrus:** Location of the primary motor cortex in the brain and the location of upper motor neuron atrophy in patients with severe ALS.
- **Babinski's reflex:** Sign of upper motor neuron damage. Seen as upgoing toes in response to a painful stimulus applied to the sole of the foot.

Werdnig-Hoffmann Disease (Infantile Spinal Muscular Atrophy Type 1)

An autosomal recessive disorder manifested by congenital hypotonia (floppy infant syndrome). It is characterized by a progressive loss of motor neurons in the anterior horns of the spinal cord, resulting in atrophy of anterior spinal roots and peripheral motor nerves and denervation in multiple skeletal muscle groups. Death occurs before 1 year.

Pick's Disease (Frontotemporal Dementia)

Atrophy of the frontal and temporal areas of the brain (can be seen on CT) affecting people between the ages of 40 and 60 who initially present with personality changes (behaving poorly in public), speech difficulty (aphasia), and parkinsonian traits. Pathologic lesions called Pick's bodies (neurons with tau protein collections) are seen. Treatment is supportive.

Friedreich's Ataxia

Inherited, autosomal recessive disease that causes progressive demyelination of the spinal cord and peripheral nerves. Manifests in children (aged 5–15 years) as difficulty walking (ataxia) that progresses to weakness in the upper extremity. Slurring and slow speech (dysarthria) are late signs. Associated with heart anomalies and disease.

BRAIN LESIONS

The brain organizes many tasks into specific anatomic locations (e.g., vision, motor movement, and speech). A lesion to any given area will cause a characteristic set of deficits. Knowledge of these areas are high yield in answering questions and in clinically identifying the location of the lesion (see Table 6-40).

TABLE 6-40. Areas of the Brain and Their Associated Deficits

Area	Deficit
Broca's area	Motor aphasia with good comprehension.
Wernicke's area	Sensory aphasia with poor comprehension.
Arcuate fasciculus	Conduction aphasia; poor repetition with good comprehension and fluent speech.
Amygdala (bilateral)	Klüver–Bucy syndrome (hyperorality, hypersexuality, disinhibited and behavior).
Frontal lobe	Personality changes and deficits in concentration, orientation, and judgment.
Right parietal lobe	Spatial neglect syndrome (agnosia of a given side of the environment).
Reticular activating	Coma.
Mammary bodies (bilaterally)	Wernicke–Korsakoff syndrome.
Basal ganglia	Resting tremor, chorea, or athetosis.
Cerebellar hemisphere	Intention tremor, limb ataxia.
Cerebellar vermis	Truncal ataxia, dysarthria.
Subthalamic nucleus	Contralateral hemiballismus.

Demyelinating Diseases

Multiple Sclerosis

Demyelinating disease of the CNS, typically presenting in young adults (18–40 years of age) as visual disturbances, paresthesias, spasticity, speech disturbances, or gait abnormalities. These neurologic deficits wax and wane and involve different areas of the CNS. Evidence suggests it is an autoimmune disease involving T-cell and antibody-mediated injury to myelin sheaths and/or oligodendroglial cells.

- **Plaques:** MS is characterized by the presence of multiple areas of demyelination, termed **plaques**. Common sites include periventricular white matter, optic nerves, and spinal cord white matter.
- **Shadow plaques:** Contain axons invested by abnormally thin, faintly staining myelin sheaths and are believed to represent areas of remyelination.

- **Oligoclonal band:** Gamma globulin is increased, and CSF electrophoresis reveals discrete bands of immunoglobulins known as **oligoclonal bands.**
- **Myelin basic protein:** Suggested target of autoantibodies and T-cell activity. Often present in the CSF during periods of active demyelination.

Guillain-Barré Syndrome

This syndrome can follow a viral or mycoplasma infection, allergic reaction, or surgical procedure. It is characterized by rapidly progressive ascending motor weakness that may lead to death from respiratory failure. Sensory deficit is less pronounced,

Progressive Multifocal Leukoencephalopathy (PML)

Progressive demyelination of the CNS caused by JC virus in immunocompromised patients (AIDS, lymphoma). Presents with a range of symptoms (hemiparesis, aphasia, dysarthria, hemianopsia). MRI and CT show multiple lesions in the white matter.

SEIZURES

Result from abnormal neural activity at either a single focus (partial) or globally (generalized). They will present in a range of ways (sensory perceptions, unintentional motor movement, loss of consciousness, auras), depending on the location of the abnormal foci within the brain. Keys to diagnosis involve the age of the patient, presence or absence of loss of consciousness, and characteristics of the event (types of movements, auras). EEG is the first-line test.

Partial

Simple

Seizure lasts 10–30 seconds and is characterized by movements of the head, neck, or extremities. Consciousness is maintained, There is no postictal confusion. EEG shows a multifocal spike pattern.

Complex

May begin as a simple seizure but progresses to loss of consciousness. The event may be preceded by an aura. Followed by repeated movements (purposeful or nonpurposeful) or repeated words or moans.

Generalized

Absence

Attacks described as staring spells in children aged between 3 and 5 years (the child stops the task at hand and stares). There is no postictal state or tonic-clonic movement, and children do not remember the event. EEG findings show a 3-Hz spike-and-wave pattern. First-line treatment is ethosuximide.

Tonic-Clonic (Grand Mal)

Loss of consciousness, bilateral extremity movement (tonic-clonic movements), and often urinary incontinence and tongue biting. The patient is confused in the postictal state.

INTRACRANIAL HEMORRHAGE

Epidural Hematoma

Most frequently caused by **middle meningeal artery rupture** secondary to skull fracture. These hematomas **rapidly expand** and increase intracranial pressure, leading to flattening of the gyral crests, herniation, brain stem compression, and death. The patient will often lose consciousness, regain it and have a lucid period, but then lose consciousness again. CT will show a biconcave disk–shaped collection of blood. Surgical intervention is needed immediately.

Subdural Hematoma

Collection of blood between the dura and arachnoid mater most often caused by rupture of **bridging veins** in association with rapid changes in head velocity (e.g., shaking or whiplash). CT will show a crescent-shaped collection of blood that crosses suture lines. Divided into acute and chronic types.

- **Acute:** Associated with a clear history of trauma, preserved gyral contours, and contain **clotted blood**. The onset of symptoms is slower than that of epidural hematoma. With time, it progresses to the chronic form.
- **Chronic:** Composed of **liquefied blood** separated from the inner surface of the dura and underlying brain by **neomembranes** composed of granulation tissue and collagen. Clinical symptoms show slowly deteriorating mental status.

Subarachnoid Hemorrhage

The most common cause of spontaneous subarachnoid hemorrhage is rupture of a saccular (berry) aneurysm. Common presenting complaints involve acute onset of headache, nausea, and vomiting. Neck rigidity and grossly bloody CSF are also present.

- **Saccular (berry) aneurysms:** Usually less than 3 mm in diameter (giant aneurysm if greater than 25 mm), and appear as rounded bulges off the arterial wall. The aneurysm's wall is composed of intima and adventitia (no media).

INTRACRANIAL TRAUMA

Concussion

Transient loss of consciousness and widespread paralysis (sometimes seizures), followed by recovery over a period of hours to days (usually with some memory loss surrounding the injury).

Diffuse Axonal Injury

These lesions result from sudden deceleration/acceleration forces that stretch or tear nerve cell processes in cerebral white matter, resulting in **axonal swelling** and formation of **axonal spheroids** (sites where axons were damaged). Causes posttraumatic dementia.

Contusions

Hemorrhages in the superficial brain parenchyma occurring in areas where the brain comes in contact with the skull. When contusions are most pronounced in the area of brain immediately under the point of impact (e.g., a hammer falls on your head), they are called **coup contusions**. When contusions occur at the areas opposite the point of injury (e.g., during falls), they are called **contrecoup contusions**.

ADULT BRAIN TUMORS

Glioblastoma Multiforme

Irregular, hemorrhagic tumors distinguished from anaplastic astrocytomas by areas of **microvascular proliferation** and **palisading necrosis** (areas of necrosis surrounded by neoplastic nuclei).

Meningioma

Tumors derived from the meningothelial cells that invest the arachnoid mater and affect **women** more than men. These tumors are firm, lobulated lesions attached to the dura mater. Calcification may be present and takes the form of **psammoma bodies**.

Schwannoma

Present as masses (**made of Schwann cells**) attached to peripheral nerves, cranial nerves, or spinal nerve roots. CN VIII (vestibulocochlear nerve) is commonly affected and is termed an **acoustic neuroma**. Schwannomas typically contain areas of densely packed spindle cells (**Antoni A tissue**), and looser, myxoid regions (**Antoni B tissue**). In denser areas, cell nuclei may form orderly palisades (**Verocay body**).

Oligodendroglioma

Present in **adults** as tumors in the cerebral hemispheres. Tumors are usually soft and well-circumscribed, and **calcification** is common. Classically, the neoplastic cells tend to cluster around native neurons, a phenomenon referred to as **satellitosis**.

Leptomeningeal Carcinomatosis

Metastatic lesions to the brain parenchyma are usually from the breast, lung, or malignant melanomas. Less commonly, they metastasize to the meninges (**leptomeningeal carcinomatosis**), which cause a vague opacification of the meninges with malignant cells present in the CSF.

PEDIATRIC BRAIN TUMORS

Pilocytic Astrocytoma

Children are more often affected, with common tumor sites including the cerebellum, third ventricle, and optic nerves. They are **less infiltrative** than fibrillary astrocytomas. Cystic areas, brightly eosinophilic **Rosenthal fiber**, and eosinophilic, protein-rich droplets (**hyaline granular body**) are often present. Treatment is surgical.

Medulloblastoma

Primitive neuroectodermal tumors (PNETs) is a group of tumors (including Ewing's sarcoma and neuroblastoma) composed of embryonal small blue cells that occur predominantly in **children**. The member of this group affecting the CNS is **medulloblastoma**. Medulloblastomas are lesions of the cerebellum (causing gait abnormalities) occurring during the first two decades of life. They are composed of small blue cells which sometimes form small rosettes (**Homer-Wright rosette**) around a fibrillar core.

Ependymoma

Ependymomas occur at any age and arise within the ventricular cavities, leading to **hydrocephalus** (usually the patient is under age 20), or in the central canal of the spinal cord (adults). Microscopically, there are elongated cells with processes radiating around blood vessels (**perivascular pseudorosette**) or lumina (**ependymal rosette**). **Myxopapillary ependymoma** is another variant encountered in the filum terminale.

Craniopharyngioma

Benign neoplasm found near the pituitary gland that arises from Rathke's pouch (developmental structure related to the primitive gut). Tumors are often cystic and contain fluid and calcifications. Symptoms present when the tumor reaches a large size and compresses nearby structures, presenting with diabetes insipidus, delayed puberty, or hypothyroid symptoms (compression of the pituitary stalk), or visual disturbances (compression of the optic chiasm). Diagnosis is made by head CT or MRI. First-line treatment is surgical resection.

Hemangioblastoma

Well-circumscribed, cystic lesions composed of delicate vascular channels and intervening lipid-laden, foamy stromal cells that occur in the cerebellum and meninges.

SPINAL CORD LESIONS

The spinal cord contains numerous tracts running from the peripheral body to the CNS and back. Each tract carries different information regarding sensation and motor function. An insult to the spinal cord will produce a characteristic presentation, depending on the specific tracts affected,

Syringomyelia

Fluid-filled neuroglial cavity within the spinal cord causing sensory loss in a cape-like distribution over the shoulders and back. The spinothalamic tract is affected, Associated with congenital neural abnormalities.

Tabes Dorsalis

Degenerative disease of the posterior columns of the spinal cord. Causes loss of position sense, vibration, and tactile discrimination. Associated with tertiary syphilis.

Brown-Séquard Syndrome

Hemisection of the spinal cord. Causes loss of motor function on one side of the body with loss of sensation on the contralateral side. Associated with trauma (e.g., knife wound), spinal cord tumor (compression of half of the spinal cord), or vascular ischemia.

Horner's Syndrome

Ptosis (drooping eyelid), miosis (constricted pupil), and anhidrosis (lack of perspiration) on one side of the face due to injury of sympathetic nerve fibers anywhere along their path from the C8–T2 ventral spinal roots to the superior cervical ganglion until termination at sites of innervation.

Anterior Spinal Cord Syndrome

Affects the anterior two-thirds of the spinal cord, but spares the posterior columns due to occlusion of the anterior spinal artery.

PERIPHERAL NERVE INJURIES, UPPER EXTREMITY

See Table 6-41.

TABLE 6-41. Upper Extremity Nerve Injuries

Nerve	Loss of Function	Associations
Brachial plexus, upper trunk	Loss of abduction, flexion, and lateral rotation of the arm ("waiter's tip" hand).	Breech delivery or fall from a horse or motorcycle; termed Erb-Duchenne palsy.
Brachial plexus, lower trunk	Atrophy of the thenar and hypothenar eminences and interosseous muscles.	Birth trauma, thoracic outlet syndrome; Klumpke's paralysis.
Radial	Loss of extension of the arm and hand; causes wrist drop.	Mid-shaft fracture of the humerus.
Median	Loss of forearm pronation, thumb opposition, and flexion of the wrist and first and second phalanges.	Supracondylar fracture of humerus; compression in the carpal tunnel.
Ulnar	Loss of abduction of ring and little finger, causing claw hand.	Medial condylar fracture of the humerus.
Axillary	Weakness in lateral rotation and abduction of the arm.	Fracture of the surgical neck of the humerus or shoulder dislocation.
Long thoracic	Paralysis of serratus anterior muscle, causing a winged scapula.	Injury during breast surgery; stab wounds.

CEREBRAL HERNIATION

Cerebral edema is the presence of increased water content **within the brain parenchyma**. Grossly, the gyri become flattened, the sulci narrowed, and the ventricles compressed. Cerebral edema can lead to herniation. The expanding brain and increased intracranial pressure within the rigid skull displaces brain tissue.

Transtentorial

The medial aspect of the temporal lobe is compressed against the free margin of the tentorium cerebelli, impinging on CN III (pupillary dilation and impaired ocular movements).

Subfalcine

Unilateral or asymmetric expansion of the cerebral hemisphere displaces the cingulate gyrus under the falx cerebri (compression of the anterior cerebral artery with ischemic injury to the primary sensory and/or motor cortex).

Tonsillar

Life-threatening displacement of the cerebral tonsils through the foramen magnum (damages respiratory centers of the medulla oblongata). It is accompanied by hemorrhagic lesions in the midbrain and pons (Duret's hemorrhages).

VISUAL FIELD DEFECTS

The brain processes sight along a pathway that extends from the retina to the visual cortex (see Figure 6-49). Lesions along this pathway produce a characteristic visual field deficit.

INFECTIOUS DISEASES

The CNS is susceptible to a range of infectious diseases that can be fatal. The typical presentation is related to inflammation, and includes headache, neck stiffness, photophobia, fever, and even focal neurologic deficits. Diagnosis is often made by cerebrospinal fluid analysis.

Meningitis

Inflammation of the meninges and subarachnoid space. Divided into acute (bacterial), lymphocytic (viral), and chronic meningitis.

- **Acute (purulent) leptomeningitis:** Nearly all cases are caused by bacteria that reach the CSF via the blood after colonizing the nasopharynx. The meninges become congested and contain creamy exudates in the subarachnoid space. Clinical presentation includes fever, headache, stiff neck, altered mental status, and turbid CSF with an increase in neutrophils and decrease in glucose.
- **Acute lymphocytic (viral) meningitis:** Typically a self-limited meningitis with a better prognosis than bacterial meningitis, although the clinical presentation is similar. The difference is in the CSF; lymphocytes are present and the glucose level is normal.
- **Chronic meningitis:** Most often caused by bacteria or fungi, including *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, and *Treponema pallidum*. Clinically, the classic meningeal signs may not be present. The

CSF is characterized by significantly elevated protein, a mononuclear infiltrate, and a decreased glucose concentration.

Brain Abscess

Staphylococci and streptococci can cause brain abscess, which usually occurs in the cerebral hemispheres and begins as areas of softening (cerebritis) that gradually liquefy. The lesions become isolated from the rest of the brain and contain green-yellow pus. Clinically, they present with fever, neurologic deficit, and increased cranial pressure.

Viral Encephalitis

Generalized infection of the brain parenchyma associated with viral infections (which can cause inclusion bodies). If the viral encephalitis is associated with leptomeningitis, it is designated as meningoencephalitis. Perivascular inflammatory infiltrates are characteristic of most types of viral encephalitis. Localized aggregates of microglial cells (microglial nodules) are present and associated with phagocytosis of neurons (neuronophagia). A number of viruses can cause encephalitis.

- **Arbovirus encephalitis:** Arthropod-borne viruses (e.g, eastern and western equine encephalitis) cause these, most commonly in late summer. Prognosis is worse if it occurs at the extremes of age.
- **Herpes simplex encephalitis (HSV I):** Most common cause of sporadic viral encephalitis affecting the temporal lobes and orbital frontal area, causing hemorrhagic, necrotizing encephalitis. Treat with antivirals.
- **CMV encephalitis:** Associated with AIDS. Commonly affects the ependymal cells.
- **HIV encephalitis:** Can present shortly after seroconversion and is clinically indistinguishable from other forms of self-limited viral meningitis.

Poliomyelitis (Polio)

Poliovirus infection spread through the GI route. Reproduces in lymphoid tissue before secondary viremia spreads infection to the CNS. Mainly affects motor neurons of the anterior horn of the spinal cord. Clinical presentation is related to severity of infection.

- **Mild disease:** Viral syndrome (fever, malaise, emesis).
- **Severe disease:** Asymmetric motor paralysis with intact sensation during a febrile illness. Aseptic meningitis, urinary retention, and muscle spasm may also be seen.
- **Vaccination:** Inactivated polio virus (IPV) given in childhood stimulates circulatory antibody formation and secretory IgA antibody (blocks infection via the GI tract).
- **Oral polio vaccine (OPV):** Rarely associated with paralytic poliomyelitis.

Spongiform Encephalopathy

A group of uncommon transmissible disorders that include Creutzfeldt-Jakob (CJD) and kuru. They are caused by "infectious" proteins called prions, which are modified forms of normal structural proteins. Clinically, they present as rapidly progressive dementia accompanied by gait abnormalities and startle myoclonus.

- ***PrP* gene:** Hereditary cases are characterized by a mutant *PrP* gene that encodes a form of PrP that spontaneously changes to the structurally abnormal disease-causing protein at high rates.
- **Spongiform change:** The presence of vacuoles within the neuropil and cell bodies in gray matter. The hallmark of CJD.

- **Kuru plaques:** Amyloid-rich deposits that may be encountered in some forms of spongiform encephalopathy.
- **New-variant CJD:** Newly recognized form associated with eating the tissues of cattle infected with bovine spongiform encephalopathy. These are dominated early in their course by behavioral and psychiatric problems.

Progressive Multifocal Leukoencephalopathy (PML)

A slowly evolving encephalopathy caused by the polyomavirus JC virus, and affects the immunocompromised (e.g., AIDS). The virus infects oligodendrocytes resulting in areas of demyelination.

CNS Toxoplasmosis

Toxoplasmosis causes areas of necrosis and a mononuclear infiltrate with *Toxoplasma gondii* in the form of pseudocysts found at the margins of the necrotic areas. Frequently associated with AIDS.

VASCULAR DISEASES

More prominent in the elderly.

Global Hypoxic-Ischemic Encephalopathy

Global refers to the entire brain, **hypoxia** is decreased tissue oxygenation, and **ischemia** is decreased tissue perfusion. The causes include cardiac dysrhythmia, shock, and increased intracranial pressure. Symptoms range from transient deficit to brain death. Morphologically, signs of necrosis are present (no inflammatory reaction).

- **Arterial border zones:** Areas of the brain located at the junctions of arterial territories, and are susceptible to ischemic injury (the first areas to lose blood flow during hypotension).
- **Laminar cortical necrosis:** An irregular, linear zone of softening and discoloration in the cortical mantle, reflecting the vulnerability of specific layers of neurons to ischemic injury.

Infarcts

Caused by local interruption of blood flow (due to atherosclerosis or emboli), more common in men than women, and usually presenting in the seventh decade. Those caused by atherosclerosis (thrombosis) usually affect the internal carotid arteries, while emboli typically affect the middle cerebral artery.

- **Middle cerebral artery:** Infarcts cause contralateral hemiparesis and spasticity, loss of sensation, visual field abnormalities, and speech abnormalities (aphasia).
- **Transient ischemic attacks (TIAs):** Brief episodes (lasting from minutes to 24 hours) of neurologic dysfunction that represent self-limited vascular obstruction. They predict subsequent infarcts.

Primary Brain Parenchymal Hemorrhage

Bleeding into the brain is associated with chronic hypertension, coagulation disorders, vasculitis, and aneurysms. The peak age of incidence is 60 and it typically affects the basal ganglia. Grossly, a well-circumscribed hematoma is formed that can dissect through the brain parenchyma and cause mass effects responsible for the presenting symptoms of severe headache, vomiting, and loss of consciousness.

- **Charcot-Bouchard microaneurysms:** Minute arterial aneurysms occurring in vessels less than 300 μm in diameter, most commonly in the basal ganglia.

Vascular Malformations

There are four major types of vascular malformation, all of which can cause intracranial hemorrhage: arteriovenous (the most common), capillary telangiectases (punctate lesions of the pons and white matter), venous angiomas (thin, dilated veins in the spinal cord and meninges), and cavernous angiomas (thick-walled venous channels with dense fibrous stroma).

- **Arteriovenous:** Malformations are conglomerates of haphazardly arranged vessels of varying sizes, usually in the cerebral hemisphere, and are supplied by the middle cerebral artery. The most common clinical manifestation is hemorrhage after the first decade of life.

LEUKODYSTROPHY

A group of disorders usually seen in infancy and childhood in which an intrinsic defect interferes with the generation and/or maintenance of myelin (see Table 6-42).

Metabolic Disturbances

Wernicke–Korsakoff Syndrome

Thiamine deficiency causes this syndrome and it is most commonly associated with chronic alcoholics.

Wernicke's Encephalopathy

Characterized by fairly rapid onset of confusion, paralysis of extraocular muscles, and ataxia. If untreated, Korsakoff's psychosis may result.

Korsakoff's Psychosis

Characterized by an inability to either form new memories or retrieve old ones, often accompanied by confabulation.

Subacute Combined Degeneration of the Spinal Cord

Deficiency of vitamin B_{12} causes pernicious anemia and gliosis in the nervous system. Associated with the development of this disorder is a condition charac-

TABLE 6-42. Types of Leukodystrophy

Disorder	Inheritance	Metabolic Abnormality
Metachromatic leukodystrophy	Autosomal recessive	Arylsulfatase A deficiency
Krabbe's disease (globoid cell leukodystrophy)	Autosomal recessive	Galactocerebroside B-galactoside deficiency
Adrenoleukodystrophy	X-linked and autosomal recessive	Peroxisomal defect; elevated levels of very-long-chain fatty acids

terized by myelin vacuolation in the dorsal and lateral white matter columns of the spinal cord.

Hepatic Encephalopathy

Patients with systemic derangement (like **hepatic encephalopathy**) also develop evidence of CNS dysfunction. In the brain, there is an **increase in astrocytes** related to the increase in ammonia levels due to poor liver function.

- **Asterixis:** Hepatic encephalopathy is characterized by altered levels of consciousness and a characteristic "flapping" tremor termed asterixis.

Central Pontine Myelinolysis

Condition characterized by demyelination within the basis pontis. Associated with patients who had hyponatremia corrected too rapidly.

CHAPTER 7

Psychiatry

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BASIC DEFINITIONS AND CONCEPTS

Gain

- Primary gain: What the symptom does for the patient's internal economy.
- Secondary gain: What the symptom gets the patient (attention).

Disorders of Thought Processes

Thought process describes how a patient puts his or her ideas together and communicates them to others. Disorders in thought processes include:

- Illogical ideas.
- Thought blocking.
- Short attention span.
- Clang associations (i.e., speaking in rhyming words).
- Flight of ideas (i.e., rapid succession of thoughts).
- Concretion: Patient has one-dimensional thought.
- Tangential thought: Patient gets lost on an abstract thought and loses the point of the original concept.
- Circumferential thought: Patient starts to get lost, but eventually returns to convey the original idea.

KEY FACT

Hypna**GOG**ic hallucinations occur while **GOING** to sleep.
Hypn**OP**ompic hallucinations occur while waking **UP** from sleep.

Disorders of Thought Content

Thought content is defined as the types of ideas that a patient expresses. Disorders include:

- Delusions: False beliefs that are not shared by the general population.
- Phobias: Extreme yet irrational fear of a situation or an object.
- Obsessions: Intrusive and repetitive thoughts.
- Compulsions: Repetitive behaviors.
- Suicidal/homicidal thoughts.
- Poverty or overabundance of thoughts: Too few or too many ideas.

FLASH FORWARD

Olfactory hallucinations often occur as an aura before a seizure.
Visual hallucinations are more commonly associated with medical disorders.
Auditory hallucinations are most consistent with schizophrenia.
Tactile hallucinations are common in delirium tremens (alcohol withdrawal) and in cocaine abusers (during intoxication).

Disorders of Perception

Perception is the process by which a person interprets and organizes internal and external sensations to produce meaningful experiences of his/her world. Disorders of perception occur when a patient misinterprets his/her environment (see Table 7-1).

TABLE 7-1. Definitions and Patient Scenarios of Disorders in Perception

Symptom	Definition	Patient Scenario
Illusion	Misperception of real external stimuli.	A woman who is outside in the dark thinks that the lawn chair is a tiger.
Delusion	False beliefs not shared by others. Maintained in spite of proof to the contrary. Usually fixed, unshakable, and present > 1 month.	A man tells his doctor that his landlord is poisoning him with toxic gas.
Idea of reference	False belief of being referred to by others.	A woman states that a radio show host is talking about her.
Hallucination (visual, auditory, olfactory, tactile, gustatory)	False sensory perception.	A cocaine abuser feels bugs crawling under his skin ("cocaine bugs").

TABLE 7-2. Mature Defense Mechanisms

Defense Mechanism	Characteristics	Example
Altruism	Negative feelings about self alleviated by assisting other people.	A man who has negative feelings about being abandoned by his parents as a child works at an orphanage.
Humor	Focusing on the humorous aspect of an uncomfortable or adverse situation.	A nervous patient jokes about an upcoming operation.
Sublimation	Replacing a socially unacceptable desire with an action that is similar, but is socially acceptable.	A man who has violent thoughts decides to pursue a career as a butcher.
Suppression	Voluntarily pushing uncomfortable ideas or feelings out of the conscious mind.	A student consciously chooses not to think about upcoming exams until a few days prior to the exams.

Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) Criteria

In order to be diagnosed with any mental disorder, a patient has to exhibit symptoms that conform to the criteria outlined in the DSM-IV-TR. The criteria for the diagnosis of each mental disorder are determined by the American Psychiatric Association.

Defense Mechanisms

Defense mechanisms are automatic and unconscious reactions to psychological stress. They function by keeping conflicts out of the conscious mind, and subsequently help to alleviate potential anxiety caused by these conflicts. Defense mechanisms can be categorized as immature or mature (see Tables 7-2 and 7-3). Mature defense mechanisms reflect understanding or conscious awareness, whereas immature defense mechanisms are characterized by the patient reverting back to child-like actions in an attempt to handle psychological stress.

PSYCHOTIC DISORDERS

Psychosis is defined as a disconnect from reality in which patients experience delusions, hallucinations, and disordered thinking. It can be due to psychotic disorders or be caused by substance abuse or illness.

KEY FACT

Gender differences in schizophrenia:
Onset in males: 15–25 years; onset in females: 25–35 years.
Men are less responsive to antipsychotic medications and show more social and cognitive deficits.

Schizophrenia

A chronic mental disorder characterized by episodes of psychosis and distorted behavior lasting > 6 months. It affects about 1% of the population in all ethnic groups and countries studied. Genetic factors are likely contributors, with an increased rate seen in monozygotic twins. Three neurologic factors have been associated with some patients:

- Hyperactivity of dopaminergic, serotonergic, and noradrenergic systems.
- Enlargement of the lateral and third ventricles of the brain.
- Abnormalities of the frontal lobes.

TABLE 7-3. Immature Defense Mechanisms

Defense Mechanism	Characteristics	Example
Acting out	Unacceptable thoughts or feelings are expressed through attention-seeking actions.	A 16-year-old whose parents are going through a divorce begins to skip classes.
Dissociation	Temporary change in memory, personality, or consciousness.	A solider who witnessed the murder of a friend has no memory of the incident.
Denial	Refusing to acknowledge the reality of a painful experience or situation.	A woman refusing to believe that she was recently diagnosed with cancer.
Displacement	Placing an undesirable idea or feeling onto another person.	A man who is angry at his boss comes home and yells at his children.
Fixation	Exhibiting characteristics of childish behavior.	Adult men fixated with video games.
Identification	Unconsciously mimicking someone else's behavior.	An abused child grows up to abuse his own children.
Isolation	Exhibiting a lack of emotion associated with a stressful situation.	A woman who witness a murder describes the incident with no emotion.
Projection	Attributing one's own personally unacceptable feeling(s) onto another person.	A woman who has desires to cheat on her husband is convinced that her husband is cheating on her.
Rationalization	Giving logical reasons for a negative situation in an attempt to convince self that the situation is a reasonable one; superficial insight.	A man who did not get the job that he wanted told his friends that it was a good thing because it would have been a very stressful position.
Reaction formation	Replacing a personally unacceptable emotion with an opposite attitude.	A woman who unconsciously resents her marriage constantly showers her husband with affection and gifts.
Regression	Regressing back to child-like behaviors.	A 10-year-old boy who recently moved to a new state began to have enuresis.
Splitting	Labeling people or situations as bad or good.	A patient believes that his doctor is a terrible person while his therapist is the most wonderful person in the world.

KEY FACT

Patients with predominantly negative symptoms have a worse prognosis.

Presentation

Patients demonstrate psychosis and disordered thinking. These patients generally have normal memory and are oriented to person, place, and time. The symptoms are divided into positive and negative. **Positive symptoms** are thoughts, sensory perceptions, or behaviors in a person with a mental disorder that are not seen in the normal population (see Table 7-4). **Negative symptoms** are thoughts, sensory perceptions, or behaviors that are present in a normal person but are absent in a patient with mental illness.

- Positive symptoms:
  - Delusions: For example, feelings of being followed by the police.
  - Loose associations: Patient starts talking about a topic completely unrelated to what he or she was talking about before.
  - Strange behavior.
  - Hallucinations: Hearing voices that are not really there.

TABLE 7-4. Characteristics of Subtypes of Schizophrenia

Subtype	Characteristics
Catatonic	Motor disturbances with strange posturing, incoherent speech.
Paranoid	Delusions (e.g., persecutory) but better social functioning and best prognosis.
Disorganized	Inappropriate emotional responses (emotional blunting), disheveled appearance. Severe impairment and poor prognosis.
Undifferentiated	Multiple subtype characteristics.
Residual	One or more psychotic episodes, residual flat affect, withdrawal, odd behavior or thinking, but no severe psychotic symptoms.

- Negative symptoms:
  - Social withdrawal.
  - Flat affect: Patient talks in a monotonous voice and does not show any emotion.
  - Lack of motivation.
  - Thought blocking: Patient starts talking about a topic but stops in mid-sentence and is unable to continue with what he/she was saying.
  - Poverty of speech.

DSM-IV-TR Diagnostic Criteria

To be diagnosed with schizophrenia, two or more of the following symptoms have to be present for at least 1 month:

- Hallucinations.
- Delusions.
- Disorganized speech.
- Negative symptoms.
- Disorganized behavior.
- Symptoms cause significant impairment in daily living.
- Symptoms are not due to any other medical condition or substance abuse.

Treatment

Antipsychotic agents (i.e., dopamine receptor blockers) and psychosocial interventions (family, individual, and behavioral therapy).

Prognosis

There is usually a chronic downward spiral over years with frequent noncompliance and repeating psychotic episodes. Suicide is common with > 50% attempting and 10% of those succeeding.

Other Psychotic Disorders

Psychosis, delusions, and/or hallucinations are also seen in brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, and substance-induced psychotic disorder (see Table 7-5).

KEY FACT

Men are more likely to be impaired by negative symptoms, which leads to social decline.

MNEMONIC

The 5 As of schizophrenia:

Autism: Lack of communication
Affect is blunted
Ambivalence
Associations are loose
Auditory hallucinations

KEY FACT

Positive symptoms respond well to traditional antipsychotics while negative ones respond better to atypical agents.

FLASH FORWARD

If the patient is not oriented or has memory deficits, consider a cognitive disorder (see section on cognitive disorders).

KEY FACT

Haloperidol decanoate is an example of a long-acting injectable medication that can be useful for noncompliant patients.

TABLE 7-5. Characteristics of Other Psychotic Disorders

Disorder	Characteristics
Brief psychotic disorder.	Similar symptoms to schizophrenia but last **< 1 month** and are often preceded by stressful psychosocial events or factors.
Schizophreniform disorder.	Same presentation as brief psychotic disorder but psychotic and residual symptoms **last 1–6 months.**
Schizoaffective disorder.	Schizophrenia with **mood disorder** symptoms; see mood disorders.
Substance-induced psychotic disorder (schizophrenic-like psychosis).	Related to the use of stimulants, hallucinogens, or withdrawal from sedatives; usually visual or tactile hallucinations and delusions.

FLASH FORWARD

The dexamethasone suppression test can be used in the diagnosis of depression. Dexamethasone is a synthetic glucocorticoid that acts on the pituitary gland via a negative feedback loop to decrease the levels of ACTH. However, in some patients with depression, administration of dexamethasone does not lead to a decrease in ACTH.

MOOD DISORDERS

Mood is defined as one's internal emotional state which is affected by internal and external stimuli. Normally people have control over their moods, but patients with mood disorders lose this control. Uncontrollable emotions cause significant distress for these patients, and results in problems in their occupational and social lives. There are no ethnic differences in their occurrence but, due to disparities in health care availability, patients in lower socioeconomic classes often progress so far that they are misdiagnosed as schizophrenics. The lifetime prevalence for major depressive disorder is about two times higher in women, while bipolar disorder is about equal across the sexes.

There are several biological and psychosocial factors contributing to the etiology:

- Altered neurotransmitter activity (e.g., depression is associated with **decreased** levels of serotonin, norepinephrine, and probably dopamine; bipolar disorders (i.e., mania) are related to **increased** norepinephrine levels).
- Limbic-hypothalamic-pituitary-adrenal axis abnormalities.

Presentation

There are several symptoms of both depression and mania.

MNEMONIC

Depressive symptoms are SIG E CAPS:

Sleep disturbances (e.g., hypersomnia or insomnia; early morning awakenings)
Loss of **I**nterests (i.e., anhedonia)
Guilt or feelings of worthlessness
Loss of **E**nergy
Loss of **C**oncentration
Appetite changes/weight changes (usually decreased)
Psychomotor retardation or agitation (i.e., slowness or restlessness)
Suicidal ideation

MNEMONIC

Manic symptoms are DIG FAST:

Distractibility
Insomnia (decreased need for sleep)
Grandiosity
Flight of ideas
Increased **A**ctivity/psychomotor agitation
Pressured **S**peech (non-stop flow of speech)
Thoughtlessness/pleasure seeking
Excessively elevated mood
Decreased judgment

Diagnosis

There are several categories of mood disorders with different diagnostic criteria.

- **Depressive episode:** Five of the symptoms described above in SIG E CAPS, including depressed mood or anhedonia, lasting for 2 weeks.
- **Major depressive disorder:** Recurrent depressive episodes (two or more), each lasting >2 weeks with a symptom-free episode lasting 2 months. A depressive episode is characterized by five of the symptoms described in the mnemonic SIG E CAPS, and must include depressed mood or anhedonia.
  - Major depressive disorder with melancholic features: Severe depression with profound sad/ dysphoric mood. Associated with vegetative signs, agitation.

- **Bipolar I disorder:** Characterized by episodes of both mania and depression:
  - A manic episode is characterized by elevated or irritable mood lasting 1 or more weeks with three or more of the above criteria for mania.
  - May be diagnosed following one manic or hypomanic episode.
  - High rate of suicidality.
- **Bipolar II disorder:** Periods of **hypo**mania (not as severe as mania—mood disturbance not severe enough to cause social or occupational impairment; no psychotic features) and depression.
- **Dysthymic disorder:** Mild depression most of the time for 2 years. These patients cry frequently.
- **Cyclothymic disorder:** Cyclic mood shifts between dysthymia (mild depression) and hypomania for at least 2 years.
- **Seasonal affective disorder:** Depression for at least 2 consecutive years during the same season and periods of depression are followed by nondepressed seasons.

TREATMENT

- **Major depressive disorder:** Electroconvulsive therapy (ECT) is the preferred treatment for patients refractory to other treatments. The patient must be hospitalized if he/she is at a risk for suicide, homicide, or is unable to take care of self. Pharmacotherapy includes antidepressants (e.g., SSRI, TCA, MAOI). Psychotherapy (i.e., behavioral therapy) has also been shown to be effective in some patients.
- **Bipolar I or II disorder:** Medications for treatment of this disorder include lithium (a mood stabilizer), anticonvulsants, or antipsychotics (i.e., olanzapine). Psychotherapy and ECT have also been shown to be effective.
- **Dysthymic disorder:** The most effective treatment is insight-oriented and psychotherapy; however, antidepressants can also be used.
- **Cyclothymic disorder:** Similar to antimanic treatments used for bipolar disorders.
- **Seasonal affective disorder:** Light therapy, antidepressants, or psychotherapy.

PERSONALITY DISORDERS

There are 10 personality disorders that are categorized into 3 clusters (as defined by DSM-IV-TR) based on similar characteristics.

- **Cluster A (mad or weird):** Familial association with psychotic disorders (see Table 7-6).
- **Cluster B (bad or wild):** Familial association with mood disorders (see Table 7-7).
- **Cluster C (sad or worried):** Familial association with anxiety disorders (see Table 7-8).
- **Personality disorder not otherwise specified (NOS):** Passive aggressive personality disorder, sadistic personality disorder, sadomasochistic personality disorder.

Personality disorders are caused by patterns of enduring, inflexible, and maladaptive personality traits. These traits/disorders cause impaired social and/or occupational functioning. Patients are often unaware they suffer from the disorder (ego-syntonic); therefore they do not seek psychiatric help and do not do well in psychotherapy. The pattern of disorder is usually established by adolescence and is associated with other complications such as violence, depression, psychotic episodes, and suicide. This disorder affects 10%–20% of the popula-



MNEMONIC

Schizoids avoid (avoid reality, and may daydream or be cold and introverted).
Schizo**typals** are odd, magical **TYPES**.



MNEMONIC

Symptoms of borderline personality:

PRAISE

Paranoid ideas
Relationship instability
Abandonment fears, anger outbursts
Impulsiveness
Suicidal gestures
Emptiness

KEY FACT

Half of children with conduct disorder go on to have antisocial personality disorder as adults.

TABLE 7-6. Characteristics of Cluster A Personality Disorders

Type and Example	Etiology	Clinical Symptoms	Treatment
Paranoid	Small increased risk in relatives of schizophrenics.	▪ Distrust and suspiciousness; believe other are plotting to harm or deceive them. ▪ Quick to interpret events or remarks as threatening (sensitive) ▪ Emotionally distant. ▪ Differential: Paranoid schizophrenia; paranoid personality disorder patients do not have fixed delusions and are not psychotic.	▪ Psychotherapy. ▪ Short-course antipsychotics to treat psychosis.
Schizoid	▪ Increased risk in relatives of patients with schizophrenia or schizotypal personality disorder. ▪ There is a theory that neglectful parenting plays a role.	▪ Voluntary social withdrawal—"loners." Does not have nor desire close relationships or sexual encounters. ▪ Chooses to engage in solitary activities, indifferent to others, avoid personal contact. ▪ Flattened affect and emotionally detached. ▪ Differential: Paranoid schizophrenia (no fixed delusions in schizoid personality disorder, and no frank psychosis). ▪ Differential: Schizotypal personality disorder (schizoid patients are less eccentric and do not demonstrate magical thinking).	Psychotherapy.
Schizotypal	▪ Increased risk in first-degree relatives of schizophrenics.	▪ Symptoms similar to schizophrenia but less severe. ▪ Odd thought patterns, behavior, and beliefs. Magical thinking (not as severe as schizophrenics). ▪ Paranoid ideation. ▪ Ideas of reference. ▪ Inappropriate/constricted affect. ▪ Lifetime suicide rate is 10%. ▪ Differential: Paranoid schizophrenia (schizotypal patients are not grossly psychotic). ▪ Differential: Schizoid personality disorder (schizotypal patients are more magical and eccentric, and schizoid patients avoid people, whereas people avoid schizotypal patients).	▪ Psychotherapy. ▪ Low-dose antipsychotics.

KEY FACT

In obsessive-compulsive personality disorder **(OCPD)** the symptoms are ego-syntonic (i.e., behavior and thoughts are acceptable and consistent with how the patient views him-/herself), while in **obsessive-compulsive disorder (OCD),** the symptoms are ego-dystonic (i.e., the patient realizes that his/her behavior is unreasonable).

tion and up to 50% of patients in the inpatient setting. The patient must be > 18 years of age to be diagnosed with a personality disorder.

Cluster A (Weird or Mad)

Patients with cluster A personality disorders avoid social situations and are **unable to develop meaningful relationships.** They do not have psychotic symptoms and are often viewed as weird.

Cluster B (Bad or Wild)

Patients with cluster B personality disorders exhibit emotional lability. They are dramatic, emotional, unstable, and have a higher incidence of substance abuse. They are often seen as "bad" or "wild." Cluster B personality disorders are often familial, and have a genetic association with mood disorders.

TABLE 7-7. Characteristics of Cluster B Personality Disorders

Type	Etiology	Clinical Symptoms	Treatment
Borderline	▪ Five times more common in first-degree relatives of borderline patients. ▪ Increased risk in relatives of alcoholics and patients with mood disorders. ▪ Sexual or physical abuse could play a role. ▪ Childhood neglect and abuse can be predisposing factors.	▪ Forms intense but unstable relationships. ▪ Fear of abandonment. ▪ Impulsive. ▪ Feelings of emptiness or boredom and unstable sense of self. ▪ Unable to control anger, impulses. ▪ Suicidal gestures (no intent to commit suicide, but may dangerously take gestures too far). ▪ Self injury (e.g., cutting of arms). ▪ Splitting (i.e., alternating between extremes of idealization and devaluation). ▪ *Differential: Schizophrenia, mania (borderlines are not frankly psychotic).*	▪ Psychotherapy. ▪ Group therapy. ▪ Dialectical behavioral therapy. ▪ Cognitive-behavioral therapy. ▪ Low-dose antipsychotics or antidepressants (avoid benzodiazepines because of abuse potential). ▪ Medications are more effective in borderline disorder than any other personality disorder.
Antisocial	▪ Increased risk in relatives of patients with antisocial personality disorder. ▪ Violent, criminal environment leads to greater risk of developing antisocial disorder. ▪ Begins in childhood as conduct disorder.	▪ Does not conform to societal laws (has criminal behavior). ▪ Disregard for rights of others. ▪ Remorseless, reckless. ▪ Deceitful, aggressive, and impulsive. ▪ Fire setting, animal cruelty, enuresis. ▪ Differential: Drug abuse (important to consider which comes first, because behavior may be attributable to addiction).	▪ Control of behavior (prison or psychiatric hospital). ▪ Psychotherapy. ▪ Caution with medications because of high addiction potential in these patients.
Narcissistic	Not known.	▪ Exaggerated sense of self-worth and entitlement. Willing to exploit others for personal gain. ▪ Arrogant, demands attention. ▪ Lack of empathy for others. ▪ Low self-esteem underlies outward inflated sense of self. ▪ Differential: Antisocial personality disorder (both exploit others, but narcissistic patients want status versus antisocial patients want material gain or subjugation of others).	Psychotherapy.
Histrionic	▪ Genetic link to antisocial personality and somatization disorder.	▪ Need to be the center of attention. ▪ Inappropriately seductive and flirtatious (use physical appearance to attract attention). ▪ Considers relationships to be more meaningful than they really are (assumed intimacy). ▪ Unable to maintain intimate relationships. ▪ Defense mechanism of regression, an immature defense in which the person returns to an earlier libidinal phase in order to avoid conflict. ▪ Differential: Borderline personality disorder (those with BPD are more likely to be depressed or commit suicide, and histrionic patients are more functional).	Psychotherapy.

TABLE 7-8. Characteristics of Cluster C Personality Disorders

Type	Etiology	Clinical Symptoms	Treatment
Avoidant	Not known	▪ Extreme fear of humiliation and rejection from others which leads them to avoid interpersonal contact. ▪ Feels inferior to others. ▪ Differential: Schizoid personality disorder (schizoids have no desire for companionship). ▪ Differential: Social phobia **situations** are scary because of **embarrassment** versus avoidant patients: **Interpersonal contact** is scary because of **fear of rejection.** ▪ Differential: Dependent personality disorder (both cling to relationships; however, avoidant patients are slow to get involved, but dependent patients aggressively seek new relationships).	▪ Psychotherapy. ▪ Systematic desensitization. ▪ Cognitive therapy. ▪ β-Blockers to control anxiety symptoms.
Dependent	Not known	▪ Extreme need to be dependent on others for emotional support. ▪ Unable to make own decisions (need advice and assurance from others). ▪ Poor self-confidence. ▪ Fear of being deserted or alone. ▪ May tolerate abuse by a partner to avoid the situation of being left alone. ▪ Differential: Avoidant personality disorder. ▪ Differential: Borderline and histrionic personality disorders (both are dependent on other people, with dependent patients having long-lasting relationships, versus borderline or histrionic patients, who cannot maintain lasting relationships).	▪ Psychotherapy. ▪ Assertiveness training. ▪ Group therapy. ▪ Cognitive therapy.
Obsessive compulsive personality disorder	Not known	▪ Perfectionism, attention to detail. ▪ Hinder ability to complete tasks. ▪ Devoted to work. ▪ Inflexible. ▪ "Packrat." ▪ Cold and rigid in intimate relationships. ▪ Differential: OCD (OCD patients have **recurrent** obsessions or compulsions and are ego dystonic). ▪ Differential: Narcissistic (both are assertive and high achievers, but NPD patients are motivated by status, while OCD patients are motivated by work itself).	▪ Psychotherapy. ▪ Cognitive therapy.

KEY FACT

Schizoid patients avoid social interaction because they have no desire for such interactions. Avoidant patients want to have social interactions but their extreme fear of social humiliation prevents them from having any kind of social interaction.

Cluster C (Sad or Worried)

Patients with cluster C personality disorders appear to be anxious and are fearful. There is a genetic association with anxiety disorders. They are often seen as "worriers."

ANXIETY DISORDERS

Anxiety is defined as a state of apprehension, terror, and fear in response to an external threat.

Anxiety becomes pathologic when:

- Reaction is out of proportion to the severity of the threat.
- Anxiety interferes with daily living.

Anxiety disorders are common, with a prevalence of 30% in women and 19% in men.

Panic Disorder With or Without Agoraphobia

The defining feature of panic disorder (PD) is unexpected and recurrent episodes (twice or more per week) of panic attacks that develop abruptly and last ~ 30 minutes (reaching a peak in 10 minutes). There is a strong genetic component; first-degree relatives of patients with PD have a four to eight times greater risk of developing PD. Patients with PD have dysregulation of the autonomic nervous system, CNS, and cerebral blood flow.

Panic Attacks

Presentation

- Shortness of breath
- Chest pain/discomfort
- Palpitations/increased heart rate
- Sweating, shaking
- Nausea/abdominal discomfort
- Feelings of choking, going crazy, losing control, or dying
- Constantly afraid of having additional attacks
- Numbness/tingling
- Chills/hot flashes
- Light-headedness
- Depersonalization

DSM-IV-TR Diagnostic Criteria

Recurrent panic attacks occur in which the trigger is not known. The patient experiences at least one of the following for 1 month:

- Constant worry about having additional attacks.
- Very concerned about the implications/consequences of attacks (e.g., "going crazy," losing control).
- Daily functioning has been severely affected by symptoms.

Agoraphobia

PD can occur with or without agoraphobia. Agoraphobia is extreme fear of being in a place where escape is difficult. Both PD with and without agoraphobia are more common in women, with average age of onset of 25. The condition is chronic and attacks can be triggered by psychological stressors.

DSM-IV-TR Diagnostic Criteria

Great anxiety about being in a situation where escape is difficult in the event of a panic attack. The patient avoids the situation, endures it with great anxiety, or needs someone to accompany them. Symptoms are not attributed to another mental disorder.

Treatment

- **Behavioral therapy:**
  - Relaxation techniques
  - Cognitive-behavioral therapy (i.e., exposure/desensitization therapy)
  - Psychotherapy
- **Pharmacotherapy:**
  - Antidepressants: SSRI, TCA, or MAOI (an SSRI is first-line treatment for agoraphobia)
  - Benzodiazepines

FLASH BACK

Anxiety involves the amygdala and is associated with increased activity of norepinephrine and decreased activity of GABA and serotonin.

KEY FACT

Many of the symptoms of panic attacks are similar to those of myocardial infarction (MI) and the possibility of MI has to be ruled out. If the symptoms are due to a panic attack, the patient's ECG and cardiac enzymes will be within normal limits.

MNEMONIC

Criteria for panic attack:

PANIC
Palpitations
Abdominal distress
Numbness, nausea
Intense fear of death
Choking, chills, chest pain

KEY FACT

Patients with PD with or without agoraphobia also have a higher risk of developing depression, substance abuse, phobias, and OCD.

KEY FACT

Start an SSRI at a low dose and slowly increase the dose to prevent activation side effects of SSRIs.

Phobias (Social and Specific)

Social phobia is an extreme fear of social situations in which an individual has to interact with unknown people or is subject to scrutiny by others, thus resulting in embarrassment or humiliation. The most common types of social phobia are public speaking and public washroom use. Social phobia occurs equally in males and females.

Specific phobia is the most common mental health problem and is characterized by an extreme but irrational fear of a specific object or situation. The object or situation that elicits the fear can be categorized into:

- Situational (e.g., closed spaces)
- Animal/insect/environment (e.g., cats, spiders, heights)
- Other (e.g., injections, blood)

Women are twice as likely then men to have specific phobias.

Both social and specific phobias may have a genetic component since they tend to run in families. Specific phobias may be connected to a traumatic event. Overproduction of adrenergic neurotransmitters may also be a contributing factor.

KEY FACT

Social phobia is fear of embarrassment in a certain setting, while avoidant personality disorder is an overall fear of rejection and sense of inadequacy. Patients can have both disorders concurrently.

DSM-IV-TR Diagnostic Criteria

- **Social phobia:**
  - Intense fear that is triggered by social situations in which the patient might be humiliated or embarrassed.
  - The anxiety response is immediately elicited by the situation.
  - The patient is aware that his or her reaction is excessive.
  - The patient goes to great lengths to avoid the situation.
- **Specific phobia:** Symptoms are similar to those of social phobia, with the exception that intense fear is triggered by a specific object or situation (e.g., fear of spiders [arachnophobia]).

KEY FACT

Phobias are the most common mental disorder in the United States (5%–10% of the population is affected).

Treatment

- **Social phobia:**
  - SSRI (paroxetine)
  - β-Blockers (for acute situations such as public speaking)
  - Cognitive-behavioral therapy
- **Specific phobia:**
  - Cognitive-behavioral therapy (i.e., exposure/desensitization therapy)

KEY FACT

For patients under 18, symptoms must persist for more than 6 months.

Obsessive-Compulsive Disorder

Obsessions are persistent and recurrent thoughts that cause great anxiety in which the patient tries to eliminate the anxiety by doing a certain action. The patient realizes that the thoughts are a product of his/her mind and that the response to these thoughts is exaggerated (i.e., ego-dystonic).

Compulsions are repetitive and rigid actions that are done by the patient in an attempt to eliminate anxiety. The actions are not in any way connected in a realistic way to their anxiety-triggering thoughts.

The prevalence of OCD is 2%–3%, and affects men and women equally. First-degree relatives of patients with Tourette's disorder have a greater risk of developing OCD. Genetics, psychosocial factors, and an imbalance in serotonin levels all contribute to OCD. It is also thought that there is a psycho-

social aspect to OCD. In 60% of patients, the symptoms are triggered by a stressful situation.

DSM-IV-TR Diagnostic Criteria

- Symptoms of obsession or compulsion as defined above.
- Symptoms are ego-dystonic.
- Daily living is severely affected by the disorder.

Treatment

- **Cognitive-behavioral therapy:** Exposure and response prevention (i.e., the patient is exposed to the situation, which elicits anxiety, and he/she is thus prevented from doing the corresponding action that alleviates the anxiety, and is taught relaxation techniques to ease anxiety).
- **Pharmacotherapy:** SSRI (first-line treatment); TCA (clomipramine).

KEY FACT

Patients do not need to have both obsessions and compulsions to be diagnosed with OCD, but 75% of OCD patients have both obsessions and compulsions.

Generalized Anxiety Disorder

Patients with generalized anxiety disorder (GAD) experience excessive anxiety about various aspects of their daily lives, causing severe impairment of their daily activities. GAD, often described as "free-floating anxiety," is very common and has a prevalence of 45%. It affects women more then men (2:1) and onset of symptoms often occurs before age 20. The etiology is not well defined, but it is believed that genetics and psychosocial factors play a role.

DSM-IV-TR Diagnostic Criteria

- Excessive anxiety about various aspects of life.
- Symptoms have to be present for more than 6 months and severely affect daily life.
- The patient is unable to ease the anxiety.
- The anxiety has to be accompanied by at least three of the following:
  - Feeling of being on edge
  - Easily fatigued
  - Difficulty concentrating
  - Easily irritable
  - Sleep disturbance (i.e., difficulty falling asleep, restless sleep)
  - Muscle tension

Treatment

- **Cognitive-behavioral therapy**
- **Pharmacotherapy:**
  - Benzodiazepines (short-term and low-dose)
  - Buspirone
  - SSRIs
  - Venlafaxine (extended-release)

Patients should be started first on benzodiazepines and then switched to buspirone to avoid dependency; however, buspirone takes 2 weeks to start working.

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) occurs in individuals who have experienced or witnessed a life-threatening situation and they continue to relive the memories of this experience. They commonly avoid anything that reminds them of the experience. Some patients become emotionally detached and have a restricted affect. The trauma experienced by males usually is related to combat while that of women tends to be due to physical or sexual abuse.

KEY FACT

Patients with PTSD are at a greater risk for developing depression and substance abuse.

PTSD can be preceded by acute stress disorder. Acute stress disorder is characterized by anxiety symptoms occurring within 1 month of the trauma and the symptoms lasting for < 1 month. If the symptoms last > 1 month, then the patient is diagnosed with PTSD.

DSM-IV-TR Diagnostic Criteria

- The patient witnessed or experienced a situation in which he/she felt that his/her life or the lives of others were threatened, and this experience brought about feelings of extreme fear and helplessness.
- Patient continually relives the experience in one of the following ways:
  - Recurrent and intrusive thoughts
  - Dreams
  - Objects or situations that symbolize or resemble an aspect of the traumatic experience
- The patient goes to great lengths to avoid anything that will trigger the anxiety.
- Emotionally detached/restricted affect.
- Signs of increased arousal (i.e., difficulty falling or staying asleep or concentrating; irritable; inappropriate outbursts of anger).
- Daily functioning is severely affected by anxiety.
- Symptoms present for at least 1 month.

Treatment

- **Therapy:**
  - Exposure therapy (treatment of choice)
  - Relaxation techniques
  - Support groups
  - Psychotherapy
- **Pharmacotherapy:**
  - SSRI
  - MAOI
  - TCA (imipramine and amitriptyline)
  - Benzodiazepines (for acute attacks)
  - Anticonvulsants (for nightmares and flashbacks)

SOMATOFORM DISORDERS

FLASH BACK

Primary gain: Patient is unable to externally deal with a psychological conflict and thus expresses it unconsciously as somatic symptom. Secondary gain: Patients assume the sick role for psychological gain (e.g., increased attention from others).

These are characterized by physical symptoms for which there are no medical explanations (see Table 7-9). These disorders are thought to be unconscious expressions of unacceptable feelings. Although the physical symptoms are brought on by psychosocial factors, patients believe that their symptoms are medical in nature. There is primary and secondary gain associated with the somatic symptoms but patients are unaware of the gains and do not consciously seek them out. Except for hypochondriasis, somatoform disorders are more likely to affect women (see Table 7-10). Up to 10% of primary care visits may be attributed to somatoform disorders.

Somatization Disorder

KEY FACT

It is very important to rule out any medical causes of these complaints.

Patients have numerous doctor visits complaining of recurrent and multiple physical complaints that significantly affect their daily lives. Their physical symptoms are related to multiple organ systems but have no underlying organic pathology. This is a chronic and potentially lifelong disorder in which the symptoms can worsen when the patient is exposed to certain stressors.

TABLE 7-9. Key Characteristics of Somatoform Disorders

Type of Somatoform Disorder	Key Characteristics	Buzzwords
Somatization disorder	▪ Physical symptoms related to multiple organ systems, which cannot be explained medically. ▪ Numerous visits to the doctor. ▪ No cure.	Multiple organ systems.
Conversion disorder	▪ Acute onset of neurologic symptoms brought on by a stressor with no identifiable organic cause. ▪ Patient is not concerned about the condition. ▪ Tend to recover spontaneously.	Neurologic symptoms.
Hypochondriasis	▪ Convinced that he or she has a severe disease. ▪ Unsatisfied by assurance of his or her physician. ▪ Visits many different physicians.	A particularly severe disease.
Body dysmorphic disorder	▪ Patient is obsessed about a perceived physical flaw. ▪ Try to fix with make-up or plastic surgery, but is usually unsatisfied with the results.	Perceived physical imperfection.
Pain disorder	▪ Pain at more than one site that begins abruptly. ▪ Pain cannot be explained medically.	Medically unexplained pain.

Females have a 5 to 20 times greater risk of developing a somatization disorder compared to males. There is also a greater prevalence in low socioeconomic groups.

Somatization disorder has a genetic basis, and there is a 30% concordance rate in monozygotic twins. In addition, first-degree female relatives have

KEY FACT

Half of patients with somatization disorder also suffer from another mental disorder.

TABLE 7-10. Comparison of Somatoform Disorders

Disorders	Level of Awareness	Type of Gain	Cause of Physical Symptoms
Somatization	Unaware.	Primary and secondary	▪ Physical symptoms are brought on by psychosocial factors. ▪ Patient truly believes that symptoms have a medical basis.
Factious	Aware.	Primary	▪ Symptoms are not real. ▪ Patient complains of vague symptoms that do not have a medical explanation.
Munchausen	Aware.	Primary	▪ Symptoms are not real or are real but fabricated. ▪ Patients induce symptoms in different ways (e.g., take insulin to produce hypoglycemia or add blood to urine).
Munchausen by proxy	Patient is unaware, but the caregiver may be aware.	Primary	▪ Symptoms are not real or are real but fabricated. ▪ Caregivers induce symptoms in different ways (e.g., deliberately make a patient sick or mix feces into urine).
Malingering	Aware.	Tangible gain (e.g., monetary)	▪ Symptoms are not real. ▪ Patients pretend to have symptoms (e.g., walk around on crutches and pretends that he/she has an injured leg).

a greater chance of developing somatization disorder than the general population.

DSM-IV-TR Diagnostic Criteria

- At least two GI symptoms.
- At least one neurological symptom.
- At least one symptom that is sexual or related to the reproductive system.
- At least four pain symptoms.
- Onset before the age of 30 years.
- There is no organic cause of the symptoms.

Treatment

Patients truly believe that there is an organic cause for their symptoms and thus feel the need to see their doctors and are resistant to seeing a psychiatrist. As a result, the best way to "treat" such patients is to allow them to see their doctors, but secondary gain should be minimized. Great caution should be used when prescribing medications. Psychotherapy, hypnosis, and relaxation techniques have been shown to be helpful in some patients.

Conversion Disorder

Patients have either sensory or motor symptoms (most often effecting sensory organs of voluntary muscles) that are suggestive of a neurologic deficit. Patients may appear to have an inappropriate lack of concern regarding their symptoms (i.e., la belle indifférence). Workup and physical exam will be negative.

Presentation

KEY FACT

Levels of serum lactate can be used to differentiate a real seizure from a pseudoseizure: Serum lactate is elevated after a seizure but not after a pseudoseizure.

Neurologic symptoms include:

- Blindness
- Paralysis
- Paresthesias
- Pseudoseizures
- Mutism
- Globus hystericus (i.e., feeling of a lump stuck in the throat)

KEY FACT

Many patients with conversion disorder also suffer from other mental disorders such as depression, anxiety disorders, and schizophrenia.

The onset of symptoms is usually brought on by psychological stressors. Unlike somatization disorders, patients with conversion disorder appear to be unconcerned about their condition. Conversion disorder is common but it affects women two to five times more then men. It is more common in people of low socioeconomic status, unsophisticated young adults, and in people who "doctor shop." Onset of symptoms can occur at any age but often appear in adolescence or early adulthood.

DSM-IV-TR Diagnostic Criteria

- One or more neurologic symptoms that cannot be explained medically.
- Identifiable psychological stressor that led to the onset of symptoms.
- Symptoms are not intentional.
- Daily living is severely impaired by symptoms.
- Symptoms are not caused by other mental disorders.

Treatment

Most patients will recover without any therapy. However, insight-oriented psychotherapy, relaxation techniques, and hypnosis have all been shown to be effective in some patients.

Hypochondriasis

Patients have a constant and exaggerated concern that they have a serious disease. Normal physical findings are misinterpreted by these patients to be signs of severe medical illness. While hypochondriacs constantly worry that they have a serious illness, some patients with OCD constantly worry that they will catch an illness.

Presentation

Patients believe they might be suffering from a serious disease through misinterpretation of normal physical symptoms. They are convinced that they have a serious illness and are not reassured by their doctors. As a result, they visit many different physicians to get different opinions. Symptoms can be exaggerated at times of stress. The average age of onset is 25 years and both women and men are equally affected.

KEY FACT

Eighty percent of patients also suffer from major depression or an anxiety disorder.

DSM-IV-TR Diagnostic Criteria

- Constant and exaggerated concern of a serious illness.
- The concern persists despite a normal medical evaluation.
- Symptoms are present for 6 months or more.

Treatment

There is no cure and patients are often resistant to seeing a psychiatrist. The best way to deal with these patients is to schedule frequent visits to their primary care doctor.

KEY FACT

Patients with this disorder also suffer from major depression (90%), anxiety disorder (70%), and psychotic disorder (30%).

Body Dysmorphic Disorder

An obsession with a perceived imperfection of a body part. While the imperfection is minimal or imaginary, patients feel very self-conscious and spend an excessive amount of time trying to correct the perceived imperfection, either through make-up or plastic surgery. Women are more likely to develop this disorder than men. The onset of symptoms usually begins in midadolescence.

DSM-IV-TR Diagnostic Criteria

- Obsession about a perceived flaw of a body part that causes great distress.
- Daily living is severely affected.

Treatment

Although patients use make-up or plastic surgery to correct their perceived imperfection, they are usually not satisfied with the results and continue to be preoccupied with their flaw. Fifty percent of patients respond favorably to SSRIs (fluoxetine).

KEY FACT

Hypochondriasis is when patients feel they have a **specific disease.**

Body dysmorphic disorder is when patients feel **a body part** is abnormal.

Body image disturbance is when patients feel their **whole body** is abnormal.

Pain Disorder

Patients with pain disorder complain of severe pain that cannot be explained medically. Affects those 30–40 years of age.

The onset of pain occurs abruptly and increases in severity during the first few months. This disorder can be categorized as acute (< 6 months) or chronic (> 6 months). Women are twice as likely then men to have pain disorder. The average age of onset ranges from 30 to 50 years.

KEY FACT

Patients with pain disorder have higher incidence of coexisting major depression, anxiety disorder, and substance abuse.

Etiology

Psychosocial and genetic influences. Incidence is higher in first-degree relatives.

DSM-IV-TR Diagnostic Criteria

- Pain at one or more sites.
- Pain cannot be explained medically.
- Pain causes great distress.
- Pain is associated with psychological factors.

Treatment

Transient nerve stimulation, biofeedback, hypnosis, psychotherapy, and SSRIs have been shown to help with symptoms.

FACTITIOUS DISORDERS

FLASH BACK

Primary gain: What the symptom does to improve the patient's interpersonal, social, or financial situation.

Patients deliberately (consciously) produce a medical or psychological symptom with the sole purpose of assuming a sick patient's role. There is primary gain associated with this disorder.

There is a higher incidence in males and in health care workers. The most common symptoms presented include hallucinations, depression, abdominal pain, seizures, and hematuria.

Some patients have a history of child abuse or neglect which could lead to impaired sexual adjustment and a poor sense of self. As a result, these patients feel the need to play the role of a sick patient to fulfill his or her need to be in a comforting and safe environment (i.e., hospital).

Diagnostic Criteria

Patient presents with a medical or psychological disorder that was deliberately produced with the intention of assuming a sick role. There are no associated monetary incentives.

Treatment

There is no treatment. Primary care physicians should avoid doing any unnecessary medical procedures and maintain a good relationship with these patients.

Related Disorders

Munchausen Syndrome

A form of factitious disorder predominated by physical symptoms. Patients have very specific demands (e.g., demand certain types of medications) and are experienced at producing certain symptoms (e.g., takes insulin to achieve a hypoglycemic state; mixes feces in with urine).

Munchausen Syndrome by Proxy

Another form of factitious disorder in which symptoms are deliberately producedin another person (e.g., usually a child). It is considered to be a form of abuse, though the motivation is often unconscious.

MALINGERING

Unlike factitious disorders, in which external incentives (e.g., monetary incentives) are not the primary motivator of the patient's actions, patients who malinger **intentionally** produce physical or psychological symptoms for **external gains.** They often complain of vague symptoms that only improve after

they have achieved their desired purpose. Like factious disorders it is more common in men then women.

KEY FACT

Malingering is associated with tangible gain (e.g., monetary reward), while factitious disorders are associated with psychological gain (i.e., feelings that come with being a patient).

EATING DISORDERS

Patients have a distorted body image and use different methods to try to achieve their perceived ideal body image. The etiology of eating disorders is multifactorial and includes social (e.g., cultural/occupational), biological (i.e., genetic), and psychosocial (e.g., sense of lack of control over aspects of life or history of sexual abuse) factors. Eating disorders are categorized into three categories: Anorexia nervosa, bulimia nervosa, and binge eating.

Anorexia Nervosa

Characterized by an obsession with staying thin. Patients think that they are overweight even though they are underweight and they restrict their eating or binge eat to achieve their "ideal" weight (see Table 7-11).

KEY FACT

Anorexic patients tend to be underweight (15% below normal weight), while bulimic patients maintain a normal weight.

Anorexic patients are placed into two categories based on their predominant method of achieving weight loss: Restrictive and binge eating/purging. Patients who are restrictive anorexics starve themselves and exercise vigorously. Binge eating/purging anorexic patients binge, then use purging, laxatives, or diuretics to help them lose weight. They also exercise excessively. Anorexia nervosa affects 4% of adolescents and young adults, and women are 10–20 times more at risk then men. Average age of onset is 20 years. Genetics, social, and psychosocial factors all contribute to the onset of anorexia nervosa.

DSM-IV-TR Diagnostic Criteria

- Distorted body image (thinks he/she is fat even though underweight).
- Body weight > 15% below normal.
- Obsession about gaining weight.
- Amenorrhea.

Associated Mental Disorders

The restrictive type of anorexia nervosa is associated with obsessive-compulsive traits and many of these patients are socially withdrawn. Major depression and substance abuse are associated with the binge eating/purging type of anorexia nervosa.

TABLE 7-11. Differences between Anorexia Nervosa and Bulimia Nervosa

	Anorexia Nervosa	Bulimia Nervosa
Weight	**Underweight (> 15% Below Normal)**	**Normal Weight**
Characteristics	▪ Restrictive type: Starve and exercise vigorously ▪ Binge eating/purging type: Binge then purge or use laxatives/diuretics.	▪ Purging type: Similar to binge eating type of anorexia. ▪ Nonpurging type: Fast or exercise excessively.
Mortality and prognosis	Mortality ~ 10%.	Better prognosis then anorexia nervosa.
Ego-dystonic or ego-syntonic	Ego-syntonic.	Ego-dystonic.

Medical Complications

Medical complications that are associated with this disorder include:

- Amenorrhea
- Electrolyte abnormalities (hyperkalemia, hypochloremia, alkalosis)
- Hypercholesterolemia
- Cardiac abnormalities (arrhythmias, cardiac arrest)
- Melanosis coli (due to laxative abuse)
- Leukopenia
- Osteoporosis

Treatment

If body weight is > 20% below ideal body weight, treatment includes inpatient monitoring of weight gain. Behavioral and family therapy have also been shown to be beneficial. Due to the high association with major depression, antidepressants should also be prescribed.

Prognosis

This disorder has a variable course. Some patients have complete recovery while others will have relapses or get progressively worse. Mortality rate is ~ 10% due to suicide, starvation, or electrolyte disturbances.

KEY FACT

Some bulimic patients who self-induce vomiting exhibit Russell's sign, which is abrasions and scars on the back of the hands due to manual attempts to induce vomiting.

Bulimia Nervosa

Bulimic patients have a distorted body image but usually maintain normal body weight. Binging episodes are followed by vomiting, excessive exercise, or use of laxatives or diuretics. Patients can be categorized into two subtypes: Purging and nonpurging. Purging bulimic patients predominantly engage in self-induced vomiting or use of laxatives or diuretics, while nonpurging patients exercise excessively or eat little to prevent weight gain. This disorder affects 3% of adolescents and young adults and is more common in women than in men. Bulimia nervosa is associated with mood disorders, impulse control disorders, and substance abuse.

KEY FACT

Bulimic patients are ego-dystonic, unlike anorexic patients, and are thus more likely to want and seek help.

Presentation

Medical complications associated with bulimia nervosa include:

- Electrolyte abnormalities (hyperkalemic alkalosis, hypochloremia).
- Cardiac abnormalities (arrhythmias).
- Dental erosion and reddened knuckles (Russell's sign from self-induced vomiting).
- Hypertrophy of salivary glands.

FLASH BACK

Vomiting may lead to hypokalemia, hyponatremia or hypernatremia, and metabolic **alkalosis.** Diarrhea leads to similar electrolyte disturbances as well, but causes metabolic **acidosis.**

DSM-IV-TR Diagnostic Criteria

- Episodes of binge eating (i.e., excessive eating within a 2-hour period associated with a feeling of losing control).
- Binge eating is followed by self-induced vomiting, excessive exercising, or inappropriate use of laxatives or diuretics.
- Symptoms occur at least two times a week for 3 months.
- The way in which the patient perceives self is defined by weight.

Treatment

Includes psychotherapy (both individual and group), cognitive-behavioral therapy, and antidepressants (SSRI, TCA).

Prognosis

Bulimic patients tend to have a better prognoses than anorexic patients. Patients who have onset before age 15 and are able to maintain a healthy body weight for 2 years after onset have better prognoses than patients with later age of onset and those who are hospitalized for their symptoms.

KEY FACT

Bupropion is contraindicated in patients with bulimia or anorexia nervosa because of an increased incidence of seizures.

Binge Eating Disorder

Patients have recurrent episodes of binge eating associated with severe distress. In contrast to anorexia or bulimia, however, these patients do not try to prevent weight gain through excessive exercise, vomiting, or use of laxatives and diuretics. As a result, many patients with this disorder are obese, and are thus at risk for obesity-related medical conditions such as hypertension, type 2 diabetes, and cardiac disease.

DSM-IV-TR Diagnostic Criteria

- Recurrent episodes of binge eating which are not associated with other behaviors (such as excessive exercise).
- Symptoms are ego-dystonic (i.e., the patient will eat alone because he/she is ashamed of his/her eating habits; the patient feels guilty and depressed about their behaviors).
- Symptoms occur at least twice a week for 6 months.
- Three or more of the following symptoms are present:
  - Rapid eating.
  - Eating when not hungry.
  - Consume an excessive amount of food.
  - Feeling embarrassed or guilty about their behavior; thus they will tend to eat alone.

Treatment

- Diet and exercise program
- Psychotherapy
- Behavioral therapy
- Pharmacotherapy:
  - Stimulants to suppress appetite
  - Sibutramine to inhibit reuptake of neurotransmitters

COGNITIVE DISORDERS

Result from impairment of the CNS and affect memory, attention, orientation, and judgment. The Mini-Mental State Examination is used to determine the severity of the disorder. The test involves using several questions and a scoring grid to determine a patient's mental state by testing the patient's orientation, registration, attention, recall, language, and calculation. Cognitive disorders are categorized into delirium, dementia, and amnestic disorders (see Table 7-12).

MNEMONIC

Differential for delirium:

AEIOU TIPS
Alcohol
Electrolytes
Iatrogenic (e.g., anticholinergics, benzodiazepines, anti-HTN hypertension medications)
Oxygen (hypoxia)
Uremia
Trauma
Infection
***P**oisons*
Seizures (post-ictal)

Delirium

Characterized by a disturbance in consciousness in which a patient's level of consciousness varies throughout the day. Patients are easily distracted, disoriented with respect to time and place, have language disturbances, and can also experience illusions and hallucinations. Elderly patients often manifest when "sundowning" (delirium worsening at night). Delirium is caused by an underlying medical disorder and thus correction of the underlying medical disorder will lead to resolution of symptoms. Delirium can last for days or weeks and if not corrected, it is associated with a high-mortality rate.

TABLE 7-12. Difference between Delirium and Dementia

	Delirium	Dementia
Onset	Acute (from hours to days).	Gradual.
Duration	Days to weeks.	Months to years.
Level of consciousness	Fluctuates (varies throughout the day).	Normal (does not change throughout the day).
Symptoms	Fluctuates (worse at night).	Stable.
Orientation	Impaired.	Not impaired in early stages of disease.
Memory	Dramatic decline in a short period of time.	Gradual decline over a longer period of time (recent and remote memory are impaired).
Awareness	Reduced.	Clear.
Medical status	Usually reversible (after correction of underlying medical disorder).	Most are irreversible (only 15% are reversible if caused by an underlying medical disorder).
Hallucinations	Visual hallucinations common.	Hallucinations less common.
EEG changes	Present (fast waves/generalized slowing).	None.



MNEMONIC

Causes of delirium:

I'M DELIRIOUS

Impaired delivery (of brain substrates/blood)
Metabolic
Drugs (e.g., alcohol, opiates, barbiturates)
Endocrinopathy (i.e., thyroid storm)
Liver disease
Infrastructure (of cortical neurons)
Renal failure
Infection
Oxygen
Urinary tract infection
Sensory deprivation



MNEMONIC

DELIRIUM = Changes in sensor**IUM**

Etiology

Delirium can be caused by a variety of medical disorders, including infection, trauma, hypoxia, substance withdrawal (e.g., alcohol), medications, and toxins (e.g., heavy metals). It is commonly seen in ICUs and in association with acute medical illness.

DSM-IV-TR Diagnostic Criteria

- Acute change in consciousness.
- Level of consciousness varies throughout the day (i.e., waxes and wanes).
- Change in cognition (e.g., disorientation, deficits of memory, language disturbance).
- Evidence that the change in consciousness is secondary to an underlying medical disorder.

Delirium can be categorized into two groups: Quiet and agitated. Patients with quiet dementia may appear depressed.

Treatment

- Rule out anticholinergic drug use.
- Correct the underlying medical disorder.
- Pharmacotherapy: Antipsychotics, benzodiazepines (be cautious with their use because they can cause respiratory depression and an increased risk of falls).

- The patient should be placed in a well-lit and quiet environment and in a place where there can be close observation by nurses.
- Constantly reorient patient (e.g., tell patient what time it is and where they are).
- Limit the amount of sedation given to the patient (to minimize the amount of napping).

Dementia

Characterized by impaired cognitive functions and memory that is progressive and irreversible. It is a debilitating disorder that affects mainly the elderly. Unlike delirium, the level of consciousness does not vary throughout the day. The incidence increases with age and 20% of people over the age of 80 years suffer from severe dementia. Causes of dementia include increasing age, Alzheimer's disease (50%–60%), and vascular dementia (10%–20%).

Diagnosis

Fifteen percent of patients with symptoms of dementia have a treatable and reversible cause. Some treatable causes of dementia include hypoxia, hypothyroidism, malnutrition (i.e., vitamin B_{12}, thiamine, or folate deficiency), lead toxicity, Lyme disease, meningitis, neurosyphilis, and medications. It is important to rule out these treatable causes of dementia.

Treatment

There is no cure for dementia unless it is caused by a treatable medical condition (e.g., vitamin B_{12} deficiency). Treatment, therefore, involves palliative care. Patient and family should be educated and long-term care should be discussed. In patients with behavioral or emotional symptoms, low-dose antidepressants or neuroleptics can be used. Antipsychotics can be used for paranoia or hallucinations, while benzodiazepines can be used for anxiety and agitation.

Amnestic Disorders

These disorders lead to memory impairment without impaired consciousness or other cognitive functions. Like delirium, amnestic disorders are often caused by an underlying medical disorder, including cerebrovascular accident, brain trauma or tumor, hypoxia, hypoglycemia, systemic illnesses, seizures, multiple sclerosis, herpes simplex encephalitis, and substance use (alcohol, medications). Amnestic disorders can be temporary or permanent depending on the underlying etiology.

Amnesia can be categorized into two types:

- **Anterograde:** Unable to make new memories, unable to remember things that occur after the CNS insult (e.g., Korsakoff's amnesia).
- **Retrograde:** Inability to recall old memories from before the CNS insult. Often seen with ECT.

Treatment

If amnesia is caused by a reversible medical disorder (e.g., seizures, hypoglycemia), then the disorder will resolve following treatment of the medical disorder. However, in situations in which the amnesia is permanent, it is important to discuss the patient's limitations with the patient and his/her family.

KEY FACT

Depression has to be ruled out in patients with quiet dementia.

KEY FACT

Benzodiazepines can exacerbate symptoms.

KEY FACT

Delirium is more likely to affect visual modalities, and psychosis is more likely to affect the auditory system.

FLASH BACK

Dementia is caused by Alzheimer's disease, microvascular disease of the brain (vascular dementia), Pick's disease/frontotemporal dementia, Huntington's disease, Parkinson's disease, Creutzfeldt-Jakob disease, and normal pressure hydrocephalus.

KEY FACT

Major depression can cause pseudodementia.

KEY FACT

Dementia = Memory impairment
Delirium = Sensorium impairment

DISSOCIATIVE DISORDERS

Patients have sudden, temporary loss of identity or memory for personal events. These disorders are most commonly seen in women 15–30 years of age. Dissociative disorders are often preceded by a stressful life event. A high proportion of patients with dissociative disorder have a history of trauma or child abuse (see Table 7-13).

TABLE 7-13. Key Characteristics of Dissociative Disorders

Disorder	DSM-IV-TR Criteria	Epidemiology	Course	Treatment
Dissociative amnesia	▪ ≥ 1 episode of inability to recall important personal information regarding a traumatic event. ▪ Symptoms cause significant impairment in daily living.	▪ Women > men. ▪ Younger people > the elderly. ▪ Associated with other mental disorders (e.g., major depression).	▪ Most patients regain memory over a period of days. ▪ Recurrences are uncommon.	▪ To prevent recurrence, it is important to help patients recover lost memories. ▪ Hypnosis and lorazepam are used in the interview to help patients relax and to recover memory. ▪ Psychotherapy after patient recovers memory.
Depersonalization disorder	▪ Recurrent episodes of feeling detached from body or mind (i.e., patients feel like they are observers of their own lives). ▪ Patients are aware of symptoms. ▪ Symptoms cause significant distress.	▪ Women > men. ▪ Age of onset: 15–30 years. ▪ Patients have increased incidence of other mental disorders (e.g., major depression).	▪ Chronic.	▪ Treat associated mental disorders (e.g., SSRI or antianxiety drugs for anxiety or major depression).
Dissociative fugue	▪ Inability to recall past events; therefore patients are confused about personal identity or assume new identity. ▪ Patients leave their place of residence and travel to another destination and can take on a new identity (i.e., start a new life).	▪ Onset preceded by stressful life event. ▪ Predisposing factors: Substance abuse, mental illness (e.g., major depression), head trauma.	▪ Last for a few days to years. ▪ When patient regains memory of old identity, he or she is unaware of loss of memory.	▪ Similar to dissociative amnesia.
Dissociative identity disorder (multiple personality disorder)	▪ Patient exhibits ≥ 2 distinct identities (with one personality being the dominant one). ▪ Identities frequently take control of the patient's life. ▪ Patients unable to recall details of other personalities.	▪ Women > men. ▪ Predisposing factors: Childhood abuse, sexual abuse. ▪ High incidence of other mental disorders (e.g., major depression).	▪ Patients with earlier age of onset have a poorer prognosis.	▪ Hypnosis. ▪ Psychotherapy (insight-oriented).

SUBSTANCE-USE DISORDERS

When referring to substance-use disorders it is important to differentiate between substance **abuse** and substance **dependence.**

Substance abuse is defined as a maladaptive pattern of substance use that leads to clinically significant impairment or distress for a period of at least 1 year. These patients have not yet met criteria for substance dependence. Substance abuse is manifested as any one of the following:

- Use resulting in failure to fulfill major obligations (e.g., going to work).
- Substance use in potentially dangerous situations (e.g., driving under the influence).
- Legal problems related to substance use.
- Continued use despite the knowledge that substance use results in significantly impaired social and personal life.

Substance dependence is also defined as a pattern of substance use which leads to significant impairment or distress for a period of 1 year. However, the DSM-IV-TR criteria state that a patient has to exhibit three or more of the following symptoms in a 12-month period to be diagnosed with substance dependence:

- Physical/receptor dependence effects:
  - Tolerance.
  - Withdrawal.
  - Use in larger amounts and for longer periods than intended.
- Psychological/social/behavioral effects:
  - Desire to decrease usage.
  - Spends a significant amount of time and effort to acquire the substance.
  - Neglects other aspects of life due to use (e.g., social and occupational life).
  - Continue to use the substance despite the significant impairment it causes.

Substance abuse and dependence are very common and are more prevalent in men than in women.

Sedatives

Sedatives depress the CNS by increasing the activity of GABA (an inhibitory neurotransmitter). Sedatives include **alcohol**, **barbiturates**, and **benzodiazepines.**

Alcohol

Alcohol is the most commonly abused substance. The prevalence of alcohol abuse in the United States is 7%–10% (see Table 7-14). Alcohol activates GABA and serotonin receptors in the CNS and is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase in the liver. Studies have shown that women develop alcohol-related brain damage more readily than men. This theory is known as **telescoping**, which states that chronic alcohol consumption in women leads to a later onset and accelerated negative effects on the structure and function of the brain.

Presentation

Long-term alcohol abuse can lead to **Wernicke's encephalopathy**, which is caused by vitamin B_{12} deficiency. Wernicke's encephalopathy is manifested

KEY FACT

Unlike amnestic disorders (a form of cognitive disorder), the loss of memory associated with dissociative disorders is not secondary to a medical disorder or substance abuse.

KEY FACT

Tolerance = Increased dosage of the substance is needed to achieve the desired effect.
Withdrawal = Development of a specific set of symptoms after cessation or decreased dose after prolonged substance use.

FLASH BACK

GABA receptors are inhibitory; therefore alcohol has a sedating effect.

FLASH BACK

Alcohol → Acetaldehyde (via alcohol dehydrogenase).
Acetaldehyde → Acetic acid (via aldehyde dehydrogenase).

KEY FACT

Wernicke's encephalopathy is reversible with thiamine therapy.

TABLE 7-14. Characteristics and Management of Alcohol Intoxication and Withdrawal

Substance	Intoxication	Management of Intoxication	Withdrawal	Management of Withdrawal
Alcohol (serum alcohol or breathalyzer used to determine level of intoxication)	▪ Dependent on blood alcohol levels (BAL). ▪ BAL 100–150 mg/dL = ataxic gait and poor balance. ▪ BAL of 400 mg/dL = respiratory depression. ▪ Legal limit of intoxication in most states is 80–100 mg/dL. ▪ Serum γ-glutamyltransferase (GGT) is sensitive indicator of alcohol use.	▪ Check ABCs (**A**irway, **B**reathing, **C**irculation). ▪ Intubate patients who are severely intoxicated. ▪ Monitor electrolytes, glucose levels, and acid–base status.	▪ Earliest symptoms occurs 6–24 hours after last drink. ▪ Anxiety, tremor, insomnia, irritability, tachycardia, anorexia, hyperreflexia, fever, seizures, hypertension, hallucinations (tactile/visual), delirium. ▪ Delirium tremens: Seizures with altered mental status (a medical emergency), occur 72 hours after last drink, and is associated with a high-mortality rate (15%–20%). ▪ ~ 5% of patients admitted for alcohol-related disorders (e.g., detox) progress to delirium tremens.	▪ Benzodiazepines (tapering doses). ▪ Thiamine, folic acid, and vitamins to treat malnutrition. ▪ Magnesium sulfate or carbamazepine for post-withdrawal seizures. ▪ Delirium tremens (benzodiazepines).

as ataxia, confusion, and ocular abnormalities (e.g., gaze palsies, nystagmus). If left untreated, it can progress to **Korsakoff's syndrome**, which is chronic and irreversible. Symptoms of Korsakoff's syndrome include psychosis, anterograde amnesia, and confabulation. This syndrome is associated with periventricular hemorrhage or necrosis of the **mammillary bodies**.

Alcohol withdrawal can be life-threatening, and is characterized by autonomic instability (tachycardia, tremulousness, anxiety, hypertension) followed by psychotic symptoms (hallucinations) and confusion. **Delerium tremens** may occur 2–3 days following the last drink, and are characterized by visual and tactile **hallucinations** (treat with haloperidol), agitation, **autonomic arousal**, and seizures (treat with benzodiazepines, i.e., lorazepam).

Treatment

Treatment of chronic dependence includes Alcoholics Anonymous, disulfiram (inhibits acetaldehyde dehydrogenase, conditions the patient negatively against alcohol consumption), psychotherapy, and naltrexone (to help reduce cravings). Alcohol withdrawal is treated with benzodiazepines (lorazepam) and haloperidol.

Benzodiazepines and Barbiturates

Both of these drugs are commonly abused because they are readily available. Benzodiazepines are used to treat anxiety disorders, while barbiturates are used as anesthetics and for epilepsy treatment. Both substances potentate the effects of GABA and depress the CNS.

Presentation

Symptoms of intoxication include drowsiness, impaired coordination and judgment, ataxia, mood lability, and nystagmus. Severe intoxication can



MNEMONIC

Wernicke's encephalopathy (acute phase):

COAT RACK

Confusion
Ophthalmoplegia
Ataxia
Thiamine treatment
Retrograde amnesia
Anterograde amnesia
Confabulation
Korsakoff's psychosis

KEY FACT

Patients with altered mental status due to alcohol should be treated with thiamine and glucose, with the former being given before the latter. If glucose is given first, the mammillary bodies in the brain may become further depleted of thiamine, thus precipitating to encephalopathy.

lead to respiratory depression, coma, and even death. Benzodiazepines and barbiturates can also lead to withdrawal symptoms, including insomnia, anxiety, delirium, hallucinations, tremor, nausea and vomiting, tachycardia, and sweating (autonomic hyperactivity).

Treatment

Sodium bicarbonate can be given to increase renal excretion of barbiturates. Flumazenil (a benzodiazepine antagonist) can be used in benzodiazepine overdose. After administering flumazenil, the patient must be monitored for acute withdrawal symptoms from benzodiazepines. Treatment for withdrawal includes administration of a long-acting benzodiazepine or diazepam. Seizures can be controlled with valproic acid.

Stimulants

Stimulants including cocaine, amphetamine, caffeine, and nicotine activate the CNS by increasing the concentration of dopamine. Caffeine and nicotine are the two most commonly abused stimulants.

Cocaine

Cocaine is an alkaloid extract from the leaves of the coca plant that prevents dopamine reuptake from the synaptic cleft. Use can result in life-threatening conditions such as sudden cardiac death (coronary vasoconstriction leading to MI, arrhythmia). Maternal use can lead to placental abruption (see Table 7-15).

Treatment

Overdose can be treated with urine acidification. Phentolamine and nifedipine can be used for severe HTN. Haloperidol may be used to treat psychosis. Treatment for long-term dependence includes psychotherapy, group therapy, TCAs, and dopamine agonists (e.g., amantadine).

Amphetamines

Stimulants structurally related to catecholamine neurotransmitters can be classified into two groups: Classic and substituted. Classic amphetamines

KEY FACT

Formication: Tactile hallucinations associated with alcohol **withdrawal** and cocaine intoxication, in which patients feel as if bugs are crawling on their skin ("cocaine bugs").

Alcohol intoxication and withdrawal can be fatal because the CNS-depressing GABA receptors down regulate with overuse of CNS-depressing alcohol.

FLASH BACK

Benzodiazepines affect the **frequency** of opening of GABA receptors.

Barbiturates affect the **duration** of GABA-receptor firing.

KEY FACT

Benzodiazepines and barbiturates have synergistic effects. Alcohol used in conjunction with either class of drugs also result in synergistic effects.

TABLE 7-15. Characteristics and Management of Cocaine Intoxication and Withdrawal

Substance	Intoxication	Management of Intoxication	Withdrawal	Management of Withdrawal
Cocaine (cocaine intoxication can lead to death secondary to respiratory depression and arrhythmias).	▪ Increased or decreased BP, euphoria, tachycardia or bradycardia, nausea, dilated pupils, psychomotor agitation, depression, sweating, chills, respiratory depression, seizures, arrhythmias, tactile hallucinations (formication). ▪ Prolonged use can lead to paranoia and psychosis. ▪ Causes vasoconstriction leading to MI ("cocaine chest-pain"), **placental abruption.**	▪ Mild to moderate agitation: Benzodiazepines. ▪ Severe agitation: Haloperidol. ▪ Psychosis: Haloperidol. ▪ Symptomatic support (e.g., control of hypertension and arrhythmias).	▪ Crash (occurs ~ 48 hours after last use): Fatigue, malaise, depression, suicidality, hunger, constricted pupils, vivid dreams, psychomotor agitation/retardation. ▪ Withdrawal occurs 1–10 weeks after last use.	▪ Crash is not life-threatening, therefore treatment is supportive (i.e., allow the patient to recover on their own).

KEY FACT

Severe autonomic instability resulting from benzodiazepine/barbiturate or alcohol withdrawal in chronic users can be life-threatening.

KEY FACT

Benzodiazepine overdose carries a lower risk of causing respiratory depression than do barbiturates. Barbiturate overdose is very dangerous and may be life-threatening.

KEY FACT

Cocaine blocks the reuptake of dopamine, while amphetamine causes the release of dopamine.

FLASH BACK

Dopamine has a role in the "reward" system of the brain.

(e.g., dextroamphetamine, methylphenidate, methamphetamine) stimulate dopamine release at the presynaptic termina and are used in the treatment of attention deficit/hyperactivity disorder (ADHD) and narcolepsy. Designer amphetamines (methylenedioxymethamphetamine [MDMA or "ecstasy"] and methylenedioxyethylamphetamine [MDEA] or "Eve") have both stimulant and hallucinogenic effects due to the release of dopamine and serotonin, respectively. The clinical presentation and treatment of amphetamine intoxication and withdrawal is similar to that of cocaine.

Caffeine

Caffeine is the most common psychoactive agent used in the United States. It is an adenosine antagonist that also exerts a stimulant effect on the dopaminergic system.

Consumption of 250 mg of caffeine can lead to symptoms of intoxication, which include insomnia, anxiety, restlessness, twitching, rambling speech, flushed face, diuresis, and GI disturbances. If more than 1 g of caffeine (approximately 10 cups of coffee or 20 cups of tea) is ingested, symptoms such as tinnitus, severe agitation, and cardiac arrhythmia can occur. Treatment for caffeine intoxication is symptomatic and supportive.

Caffeine withdrawal also leads to symptoms including headache, anxiety, depression, and drowsiness. Treatment is symptomatic (i.e., analgesics for headaches). To avoid subsequent episodes of withdrawal, the patient should slowly taper his/her consumption of caffeine.

Nicotine

Stimulates nicotinic receptors. Symptoms of intoxication include insomnia, restlessness, anxiety, and increased GI motility. The definitive treatment for nicotine intoxication is cessation.

Patients suffering from nicotine withdrawal exhibit signs of anxiety, dysphoria, increased appetite, irritability, insomnia, and intense craving. Behavioral counseling, nicotine patch or gum, and bupropion (an antidepressant that helps to reduce cravings) have been shown to help reduce nicotine cravings.

Opiates

Opiates, such as morphine, methadone, and heroin, stimulate μ receptors and affect sedation and analgesia. Opiates also affect the dopaminergic system, thus contributing to their addictive and rewarding effects.

Methadone, L-α-acetylmethadol acetate (LAMM) and buprenorphine, all of which are synthetic opiates, can be used to treat long-term dependence on heroin (see Table 7-16). All three, however, can also lead to physical dependence and tolerance. They are legally used to substitute for illegal opiates and to prevent withdrawal symptoms. While methadone is a μ-opioid-receptor agonist, buprenorphine is a partial opioid receptor agonist used for long-term maintenance therapy. It blocks the withdrawal symptoms and euphoric effects of heroin.

Hallucinogens (Phencyclidine and Lysergic Acid Diethylamide)

Phencyclidine (PCP or "angel dust") and lysergic acid diethylamide (LSD) are both hallucinogens; however, PCP also has anesthetic and stimulant effects (see Tables 7-17 and 7-18). PCP acts on NMDA glutamate receptors and activates dopaminergic neurons, while LSD acts on serotonin receptors.

TABLE 7-16. Characteristics and Management of Opiates Intoxication and Withdrawal

Substance	Intoxication	Management of Intoxication	Withdrawal	Management of Withdrawal
Opiates	▪ Drowsiness, CNS depression, nausea/vomiting, constipation, constricted pupils, slurred speech, seizures, respiratory depression (leading to coma/death).	▪ Overdose is life-threatening. ▪ For opiate overdose with respiratory depression treat with naloxone or naltrexone. ▪ Provide ventilatory support if needed.	▪ Not life-threatening. ▪ Dysphoria, insomnia, rhinorrhea, yawning, dilated pupils, lacrimation, weakness, sweating, piloerection ("cold turkey"), flu-like symptoms (nausea/vomiting, fever, muscle ache).	▪ Moderate symptoms: Clonidine and/or buprenorphine. ▪ Severe symptoms: Methadone (tapered over 7 days).

Neither substance produces withdrawal symptoms, but patients might experience recurrence of symptoms at a later time (i.e., "flash backs").

Other Substance Use Disorders

Marijuana

Marijuana's active ingredient is cannabis, which acts on the cannabinoid receptors in the brain, leading to inhibition of adenylate cyclase. Marijuana can be either smoked or eaten and when taken in large doses, marijuana causes euphoria, tachycardia, dry mouth, increased appetite, impaired coor-

TABLE 7-17. Characteristics and Treatment of Hallucinogen Intoxication

Hallucinogen	Symptoms of Intoxication	Treatment for Intoxication
Phencyclidine (PCP)	▪ Impulsiveness, belligerence, recklessness (e.g., breaking through a pair of handcuffs), psychosis, impaired judgment, ataxia, hypertension, hyperthermia, tachycardia, rotatory **nystagmus** (pathomnemonic for PCP intoxication), high tolerance to pain, agitation, **violent behavior.**	▪ Check BP, temperature and electrolyte levels. ▪ Acidify urine with ascorbic acid (vitamin C) and ammonium chloride. ▪ Give diazepam for seizures and muscle spasms. ▪ Give benzodiazepines or dopamine antagonists for agitation. ▪ Give haloperidol for agitation or psychotic symptoms.
Lysergic acid diethylamide (LSD).	▪ Pupil dilation, tachycardia, perceptual changes, hallucinations, sweating, palpitations, tremors, impaired coordination. ▪ In high doses, paranoia (treatment involves "talking someone down"), depersonalization, anxiety.	▪ For mild symptoms, patients can be reassured. ▪ For severe symptoms, benzodiazepines and antipsychotics can be used.

FLASH BACK

Nicotine stimulates nicotinic receptors in autonomic ganglia.

FLASH BACK

Endogenous opiates include endorphin and enkephalins.

KEY FACT

The classic triad of opiate overdose includes:
- Respiratory depression
- Altered mental status
- Miosis ("pinpoint pupils")

KEY FACT

Naloxone = IV route of administration
Naltrexone = PO route of administration

KEY FACT

Both PCP and LSD alter a person's perception and PCP intoxication leads to impulsiveness, belligerence, psychosis, and violent, even homicidal behavior.
LSD intoxication leads to anxiety or depression.

TABLE 7-18. Review of Pupillary Response to Substance Intoxication or Withdrawal

Substance	Pupillary Dilation	Pupillary Constriction
Amphetamines	Intoxication	Withdrawal
Cocaine	Intoxication	Withdrawal
LSD	Intoxication	
Opioids	Withdrawal	Intoxication (pinpoint pupils)
Methadone	Withdrawal	Intoxication
Heroin	Withdrawal	Intoxication
Alcohol	Withdrawal	

KEY FACT

Withdrawal from PCP intoxication can lead to sudden onset of random homicidal violence.

dination, and conjunctival injection. Only symptomatic and supportive treatment is available for intoxication.

KEY FACT

Use of marijuana does not lead to withdrawal or dependence because tetrahydrocannabinol (THC) is a lipid-soluble drug and thus is slowly released.

SLEEP DISORDERS

The reticulate activating system modulates arousal/wakefulness. Sleep disorders are very common and affect approximately one-third of people in the United States. Sleep disorders are classified as either primary or secondary. Secondary sleep disorders are caused by another disorder (e.g., mental or medical disorder or substance abuse). Primary sleep disorders are not associated with other disorders, and are categorized into either dyssomnias or parasomnias (see Tables 7-19 and 7-20).

FLASH BACK

Elevated levels of dopamine or norepinephrine lead to decreased total sleep time.
Melatonin accumulation allows for sleep onset to occur.

Dyssomnias

Dyssomnias are primary sleep disorders characterized by impairment in the amount, quality, or timing of sleep. There are various disorders that fall into this category: Primary insomnia, primary hypersomnia, narcolepsy, circadian rhythm sleep disorder, and sleep apnea (see Table 7-21).

KEY FACT

Buzz words for narcolepsy:
- Hypnagogic hallucinations
- Hypnopompic hallucinations
- Short REM sleep
- Cataplexy
- Sleep paralysis

Parasomnias

Parasomnias are also primary sleep disorders characterized by abnormal behavior during the sleep cycle. Disorders that fall into this category include nightmare disorder, night terror disorder, and somnambulism.

Other Sleep Disorders

Restless Legs Syndrome

This is a neurologic disorder characterized by unpleasant sensations in the legs and an uncontrollable urge to move when at rest. The sensations in the legs are often described as burning, creeping, tugging, or like insects crawling inside the legs. The symptoms can begin or worsen during periods of rest or inactivity and are partially or totally relieved by movement. They typically worsen or occur only in the evening or at night, and can disturb sleep. The

TABLE 7-19. Key Characteristics of Dyssomnias

	Diagnosis	Epidemiology/Etiology	Treatment
Primary insomnia	▪ Problems falling asleep and/or staying asleep. ▪ Occurs ≥ 3 times/week for at least 1 month.	▪ Affects one-third of the population. ▪ Anxiety about not getting enough sleep exacerbates the condition.	▪ Maintain sleep hygiene (i.e., regular sleep schedule, limit caffeine intake, no daytime naps). ▪ Diphenhydramine, zolpidem, zaleplon, trazodone (short term).
Primary hypersomnia	▪ Excessive daytime sleepiness or excessive sleep for at least 1 month.	▪ Onset often in adolescence.	▪ First-line treatment is with amphetamines (stimulants). ▪ SSRIs.
Narcolepsy	▪ Sudden sleep attacks (repeated) during the day for at least 3 months. ▪ Associated with cataplexy (sudden collapse while awake, loss of voluntary muscle tone), short REM latency, sleep paralysis, hypnagogic, hypnopompic hallucinations. ▪ Immediately go into REM sleep.	▪ Uncommon. ▪ Onset often during childhood or adolescence. ▪ Possible genetic association.	▪ Scheduled daytime naps. ▪ Amphetamines, methylphenidate (stimulants). ▪ SSRIs or sodium oxalate for cataplexy.
Circadian rhythm	▪ Disparity between circadian sleep-wake cycle and environmental sleep demands (e.g., jet lag, in shift work).	▪ Seen in frequent travelers, shift workers.	▪ Remission, especially in patients suffering from jet lag (in 5–7 days). ▪ Light therapy (for shift workers). ▪ Melatonin (given 5 hours before bedtime).
Sleep apnea	▪ Abnormal sleep ventilation (central or obstructive) leading to sleep disruption and subsequently to excessive daytime sleepiness. ▪ Person stops breathing for at least 10 seconds repeatedly during sleep.	▪ 10% of population. ▪ Associated with obesity, pulmonary HTN, arrhythmias. ▪ Obstructive sleep apnea. Associated with snoring; seen more commonly in those 40–60 years old; male:female ratio is 8:1. ▪ Central sleep apnea: Higher incidence in patients with heart failure, EtOH use, more common in the elderly.	▪ Obstructive: Nasal continuous positive airway pressure, surgery (nasal or uvulopalatoplasty), weight loss. ▪ Mechanical ventilation.

TABLE 7-20. Key Characteristics of Parasomnias

	Diagnosis	Epidemiology/Etiology	Treatment
Nightmares	▪ Repeatedly being awaken by nightmares and recalling the details of the dream, causing distress. ▪ Occurs during REM sleep.	▪ Onset during childhood. ▪ Increased episodes during times of stress.	▪ Usually not treated. ▪ Give TCAs to suppress total REM sleep.
Night terrors	▪ Patients have repeated episodes of extreme frightfulness during sleep. ▪ Patients have no recollection of these episodes. ▪ Occurs in stage 3 or 4 of the sleep cycle.	▪ More frequent in children (boys > girls). ▪ Genetic.	▪ Usually not treated. ▪ Diazepam at bedtime.
Somnambulism (sleepwalking)	▪ Patients have repeated episodes of walking during sleep. ▪ Patients have a blank stare. ▪ Can be associated with other behaviors (e.g., dressing, talking). ▪ Patient can be awoken with great difficulty and often is confused when awoken (no recollection of episodes). ▪ Episodes occur during stage 3 or 4 of the sleep cycle.	▪ Onset during childhood (peak at 12 years old). ▪ Boys > girls. ▪ Genetic.	▪ None.

KEY FACT

Cataplexy: Sudden loss of muscle tone.
HypnaGOGic: Hallucinations as the patient is **GOING** to sleep.
HypnOPompic: Hallucinations as the patient is waking **UP** (not while in deep sleep).

KEY FACT

Obstructive sleep apnea: Ventilation is disrupted by physical obstruction (i.e., patients have respiratory effort, but airway obstruction prevents air from getting into the lungs).
Central sleep apnea: Little or no respiratory effort is made. The medulla does not respond to increasing levels of CO_2.

KEY FACT

Eighty percent of people with restless legs syndrome also have periodic limb movement disorder.

TABLE 7-21. Mental Disorders/Substance Abuse and Sleep Disturbances

Mental Disorder/ Substance Abuse	Sleep Disturbances
Depression	▪ Normal sleep onset. ▪ Early morning awakenings (i.e., waking up before the patient desires). ▪ Decreased REM latency. ▪ Increased total REM sleep. ▪ Decreased slow-wave sleep. ▪ Overall decreased sleep.
Bipolar	▪ Difficulty initiating sleep. ▪ Needs less sleep during manic episodes.
Anxiety	▪ Difficulty initiating sleep.
Caffeine	▪ Most common cause of insomnia.
Benzodiazepines	▪ Insomnia. ▪ Nightmares and other sleep disturbances, including restless legs syndrome. ▪ Nocturnal myoclonus. ▪ Hypnagogic hallucinations.
Alcohol	▪ Difficulty initiating sleep. ▪ Frequent awakenings. ▪ Decrease in sleep quality associated with daytime fatigue.

FDA has recently approved ropinirole (Requip), which is used to treat Parkinson's disease, for the treatment of restless legs syndrome.

Nocturnal Myoclonus

Nocturnal myoclonus is also called periodic limb movement disorder and it is a sleep disorder in which the patient moves the limbs involuntarily during sleep. It is related to restless leg syndrome.

This disorder can become worse when taking certain medications such as TCAs and MAOIs. Withdrawal from anticonvulsants, benzodiazepines, and barbiturates can also worsen the symptoms of this disorder. Treatment includes non–ergot derived dopaminergic drugs.

KEY FACT

In atypical depression, patients have hypersomnia along with weight gain and leaden paralysis.

CHILDHOOD DISORDERS

Diagnosing psychiatric disorders in children can be more challenging than diagnosing adult psychiatric disorders because the clinical data have to be gathered from various sources. The child, the parents, teachers, and even social workers should be interviewed. Parents are good sources of information and can give accurate accounts of the child's developmental progress, conduct, school performance, problems with the law, and family history. Teachers and social workers can also give valuable information about academic performance, peer relationships, and the child's social and family environment. Child psychiatric disorders can be categorized into groups depending on the prevalent symptom.

Pervasive Developmental Disorders

Pervasive developmental disorders are characterized by impairments in language and social skills. The disorder is recognized at an early age and there is a higher incidence in males; the male:female ratio is 3:1 (with the exception of Rett's syndrome, which affects females). Pervasive development disorders include autistic disorder, Asperger's syndrome and Rett's syndrome.

KEY FACT

Be sure to rule out hearing impairment during the first assessment of the child.

Autistic Disorder

Symptoms associated with autism are recognized early in childhood (usually before age 3) due to delayed developmental milestones. There is a high association with mental retardation, fragile X syndrome, and tuberous sclerosis. Males have a predilection for this disorder and genetics have some role in its inheritance. Children with autistic disorder exhibit impairment in three different areas: Social interaction, communication, and restricted and repetitive behaviors.

DSM-IV-TR Diagnostic Criteria

According to the DSM-IV-TR criteria, a child has to exhibit six of the following symptoms to be diagnosed with autistic disorder:

- Unable to develop peer relationships.
- Unable to express oneself through nonverbal expressions (e.g., facial expressions, gestures).
- Does not initiate or reciprocate social interactions.
- Does not appropriately reciprocate emotional interactions.
- Delayed impaired speech.
- Repetitive use of language.
- Repetitive play (e.g., continually stacking three blocks in a certain way).
- Exhibit repetitive and rigid rituals.
- Obsession with parts of objects.

MNEMONIC

AUTISTICS

Again and again (repetitive behavior)
Unusual abilities
Talking (language) delay
IQ subnormal
Social development poor
Three years of age at onset
Inherited component (35% concordance)
Cognitive impairment
Self-injury

TREATMENT

Treatment of autism focuses on management of symptoms and these include the following:

- Behavioral management.
- Special school curriculum focused on developing social skills.
- SSRI (for control of repetitive behaviors).
- Atypical antipsychotics (for treatment of bizarre behaviors, agitation, and tics).
- Stimulants (for hyperactivity).

Asperger's Disorder

Unlike autism, children with Asperger's disorder have normal to high intelligence but they have deficits in social interaction, narrowed interests, and gross motor clumsiness. This disorder is more prevalent in males but its etiology is not known.

DSM-IV-TR DIAGNOSTIC CRITERIA

According to the DSM-IV-TR criteria, patients must exhibit at least two of the following deficits in social interactions:

- Unable to develop peer relationships.
- Unable to express oneself through nonverbal expressions (e.g., facial expressions, gestures).
- Does not initiate or reciprocate social interactions.
- Does not appropriately reciprocate emotional interactions.
- Exhibit repetitive behaviors or activities.
- Exhibit preoccupation with inflexible routines.

TREATMENT

Treatment is geared towards symptom management and is similar to that outlined for autism.

Rett's Syndrome

KEY FACT

Patients with Rett's syndrome exhibit stereotyped hand movements such as clapping and wringing of hands.

Unlike the other two pervasive developmental disorders, Rett's syndrome predominates in females because it is an X-linked autosomal dominant trait. It is a very rare disorder and onset of symptoms often occurs between the ages of 5 and 48 months. Before the onset of symptoms, patients have normal brain development. Following onset of the disease, however, there is a restriction of brain grown and a subsequent regression of development.

DSM-IV-TR DIAGNOSTIC CRITERIA

- Brain development is normal in the first few months of life, followed by a restriction of brain growth (manifested as normal developmental milestones and head circumference initially, but impaired developmental milestones and decreasing head circumference later).
- Regression of development (i.e., loss of previously learned skills).
- Exhibit stereotyped hand movements (e.g., hand clapping and hand wringing).
- Loss of social interaction (could improve over time).
- Impaired gait or trunk movements.
- Impaired language and psychomotor development.

TREATMENT

There is no cure for Rett's syndrome, therefore treatment is supportive with management of symptoms.

Disruptive Behavior Disorder

Disruptive behavior disorder is characterized by behavior that does not conform to societal norms. Disruptive behavior disorder can be categorized as either conduct disorder or oppositional defiant disorder. Both disorders are more prevalent in males.

Conduct Disorder

The etiology of this disorder is multifactorial and includes child-rearing practices (e.g., lack of parental discipline), parental or familial factors (e.g., parental psychopathology), and family violence. There is an increased incidence of other mental disorders (e.g., mood disorder), substance abuse, and criminal behavior in these patients.

KEY FACT

Forty percent of children with conduct disorder will go on to develop antisocial personality disorder as adults.

DSM-IV-TR Diagnostic Criteria

Patients must exhibit the following behaviors for a period of > 1 year:

- Persistent behavior that does not conform to societal norms and violates the basic rights of others.
- Aggression towards living things.
- Destruction of property.
- Behavior causes impairment of daily functioning.

MNEMONIC

Children have **C**onduct disorder.
Adults have **A**ntisocial personality disorder.

Treatment

Children benefit the most from early intervention. Treatment is focused on behavior modification and problem-solving skills. Parents should be involved in the treatment plan and engaged in parent management training and family therapy. Antipsychotics or lithium can be used for aggression management, and SSRIs can be used to treat impulsivity, mood lability, and irritability.

Oppositional Defiant Disorder

Unlike conduct disorder, patients with oppositional defiant disorder do not violate the rights of others. Onset is in early childhood but symptoms can regress or progress to conduct disorder. Patients with this disorder have a predilection for substance abuse and have a higher incidence of comorbid mood disorders and ADHD.

DSM-IV-TR Diagnostic Criteria

Patients exhibit at least four of the following symptoms for ≥ 6 months.

- Frequently loses temper
- Disobedient
- Argues with authority figures (i.e., teachers and parents)
- Exhibits anger and resentment
- Easily annoyed
- Annoys others on purpose
- Spiteful
- Refuses to take responsibility for their actions

Treatment

Treatment is similar to that for conduct disorder.

Attention Deficit/Hyperactivity Disorder

ADHD affects 3%–5% of children and is more common in males than females. It is believed that the etiology of ADHD is multifactorial, and involves genetic contributors, psychosocial factors, toxin exposure, prenatal

trauma, and neurologic factors. The symptoms of most patients remit during adulthood but 20% of patients have symptoms that persist into adulthood.

DSM-IV-TR Diagnostic Criteria

Patients must exhibit symptoms for 6 months and onset of symptoms must occur before age 7 (see Table 7-22).

Treatment

Treatments for ADHD include psychotherapy and pharmacotherapy. Methylphenidate (Ritalin) is first-line therapy and SSRIs and TCAs can be used as adjunctive therapy. Parents should also go for parenting skills training.

Tourette's Disorder

Tourette's disorder is a severe tic disorder that involves motor (e.g., facial or hand tics) and vocal tics. Vocal tics can be categorized into either coprolalia (speaking obscene words) or echolalia (repeat words spoken to the patient). Coprolalia is uncommon in children. The onset of symptoms occurs before age 18, but symptoms can carry on into adulthood. This disorder is more common in males than females and onset usually occurs before 7 years of age. The etiology of Tourette's includes genetics and impairment in dopamine regulation. Patients have a high incidence of other mental disorders (e.g., OCD and ADHD).

KEY FACT

Patients must exhibit both motor and vocal tics to be diagnosed with Tourette's disorder.

DSM-IV-TR Diagnostic Criteria

Patients exhibit symptoms for > 1 year and have an onset prior to age 18:

- Motor and vocal tics.
- Symptoms cause significant impairment in daily living.

Treatment

Treatment includes supportive therapy and haloperidol or pimozide.

Separation Anxiety Disorder

This disorder affects 4% of children with an average age of onset of 7 years. It may be preceded by a stressful life event (e.g., divorce). Children with this disorder express great fear of being physically separated from their parents and will avoid being physically separated (e.g., the child may lie about feeling sick to avoid going to school). When they are forced to leave their parents they express great distress and worry about not seeing their parents again. Treatment includes supportive therapy, family therapy, and low-dose antidepressants for symptom management.

TABLE 7-22. Symptoms of Attention Deficit/Hyperactivity Disorder

Hyperactivity	Inattention	Impulsivity
Unable to stay seated.	Disorganized.	Interrupts or intrudes on others.
Unable to play quietly.	Unable to complete task.	Has difficulty waiting for turn.
Constantly fidgets.	Forgetful.	Blurts out answers.
Talks excessively.	Easily distracted.	
Runs around.	Constantly makes careless mistakes.	
	Does not listen when spoken to.	

TABLE 7-23. Classification of Mental Retardation

Type of Mental Retardation	IQ
Profound	< 25
Severe	25–40
Moderate	40–50
Mild	50–70

Selective Mutism

This is a rare disorder that occurs more in females than in males. The onset of symptoms is at 5 years and it is characterized by not speaking in specific situations. Like separation anxiety disorder, it can be preceded by a stressful life event. Treatment includes supportive therapy and behavioral and family therapy.

Mental Retardation

Mental retardation affects ~ 2.5% of the population and the incidence is higher in males than in females. According to DSM-IV-TR, mental retardation is defined as having an IQ of ≤ 70 in addition to having deficits in adaptive skills appropriate for the age group (see Table 7-23). Mental retardation has several causes, including genetic (e.g., Down's syndrome, fragile X syndrome), prenatal infection or toxin exposure, prematurity, anoxia, birth trauma, malnutrition, and hypothyroidism. Mental retardation is categorized based on its severity. The majority of cases are mild.

Rapid Review

Key Terms

Delirium	Acute alteration in sensorium.
Dementia	Chronic, slow decline in cognitive function.
Hallucination	Perceptions in the absence of external stimuli.
Illusion	Misinterpretations of actual external stimuli.
Delusion	False but nonbizarre beliefs (e.g., spouse cheating) that are maintained despite proof to the contrary.
γ-glutamyl transferase (GGT)	Elevation is a sensitive serum marker of alcohol use.
Hypnagogic hallucination	Hallucinations when going to sleep.
Hypnopompic hallucination	Hallucinations upon awakening.

DEPRESSIVE DISORDERS

Depression comes in many forms. The resultant impairment in daily functioning causes clinical concern. The number of symptoms present and their duration further characterize the subtype of depression.

Major Depressive Episode

At least five of the **SIGECAPS** criteria present for > 2 weeks, with one being depressed mood or loss of interest (see Table 7-24).

- **Major depressive disorder:** At least one major depressive episode, which may occur as a single episode or as recurrent episodes. May be associated with psychotic or atypical features, as well as postpartum. No manic or hypomanic symptoms.
- **Associated sleep changes:** Decreased slow-wave sleep, decreased REM latency, and early morning awakening.

Dysthymic Disorder

Presence of two of **SIGECAPS** features, more often than not, for a period of 2 years. Does not meet criteria for major depressive episode.

MANIA

Individuals may have an increase in sexual activity or go on extravagant shopping sprees. The episode must be severe enough to cause impairment in social or occupational functioning. The following symptoms must be present for ≥ 1 week:

- Inflated sense of self
- Grandiosity
- Decreased need for sleep
- Increased talkativeness
- Flight of ideas
- Racing thoughts
- Increased goal-directed behavior
- Increased involvement in pleasurable activities

TABLE 7-24. Mnemonic for Criteria of Depression

S	**S**leep changes; insomnia or hypersomnia.
I	Diminished **I**nterest or pleasure in formerly pleasurable activities.
G	Feelings of **G**uilt or worthlessness.
E	Decreased **E**nergy.
C	Decreased ability to **C**oncentrate.
A	**A**ppetite change; may be decreased or increased with weight gain or loss.
P	**P**sychomotor retardation or slowing.
S	**S**uicidal ideation or intent.

Hypomania

Some manic symptoms without impairment in functioning.

- **Cyclothymic Disorder:** At least 2 years of hypomanic symptoms alternating with periods of depressive symptoms (do not meet criteria for a major depressive episode).

Bipolar Disorder, Type I

Single manic episode without history of a major depressive episode. Often categorized according to the most recent episode (manic vs depressive subtype).

Bipolar Disorder, Type II

History of previous major depressive episode with ≥ 1 hypomanic episode. Must be without history of manic episodes.

PSYCHOTIC DISORDERS

Psychosis indicates an altered perception of reality and is a component of several psychiatric conditions.

Schizophrenia

At least two of the following symptoms must be present for at least 6 months, and cause social or occupational impairment: delusions, hallucinations, disorganized speech or behavior, and negative symptoms (flattened affect, alogia, or avolition).

- **Subtypes:** Paranoid, catatonic, and undifferentiated.
- **Schizophreniform disorder:** Same as symptoms of schizophrenia, but symptoms last more than 1 month and less than 6 months.
- **Schizoaffective disorder:** Period in which there are symptoms of a major depressive episode or manic episode, as well as the symptoms of schizophrenia (discussed above).

Brief Psychotic Disorder

Symptoms of schizophrenia lasting > 1 day and < 1 month. May occur in young people and can be associated with life stressors. Requires return to previous level of functioning.

Delusional Disorder

Nonbizzare delusions (delusions that could actually happen in real life, such as a significant other cheating) for at least 1 month duration. Occurs without functional impairment or bizarre behavior.

ANXIETY DISORDERS

May be grouped according to those that occur without exposure to a stressor or traumatic experience and those that do. Those that result from exposure to a stressor or a stress reaction are discussed in the next section. The rest of the anxiety disorders are discussed below. They are unified by the patient having some sort of anxiety, either in certain situations, or anxiety that is unrelated to a situation, but that the patient cannot control.

Panic Attack

Discrete episode (~ 10 minutes) during which the patient abruptly develops an intense feeling of fear or discomfort. Associated with symptoms of sweating, palpitations, shaking, feeling of choking, shortness of breath, chest pain, or nausea.

- **Panic disorder:** Recurrent panic attacks. The patient remains concerned about additional attacks between episodes. May occur with or without agoraphobia (anxiety about and possible avoidance of being in situations in which escape may be difficult or embarrassing).

Social Phobia

Fear of social situations in which the patient may be humiliated or embarrassed. The fear causes some degree of impairment. This may occur in public speaking situations, athletic events, or other social situations such as being in a crowded restaurant or in church.

Specific Phobia

Unreasonable amount of fear regarding certain situations or objects (i.e., heights, flying, or spiders). Thoughts about the situation may produce anxiety. The patient often recognizes the fear to be unreasonable. Must cause some degree of impairment.

Generalized Anxiety Disorder

Uncontrollable anxiety or excessive worry occurring more often than not for **at least 6 months.** Anxiety results in restlessness, irritability, easy fatigability, muscle tension, difficulty concentrating, and sleep disturbance.

Obsessive-Compulsive Disorder

Presence of obsessions, compulsions, or both that the individual recognizes as excessive or unreasonable, and that causes marked distress or interference with the person's normal routine.

- **Obsessions:** Recurrent thoughts or impulses that cause anxiety or distress. Examples include recurrent thoughts of injury occurring to one's loved ones despite knowing they are safe, or driving a car and thinking that one might have struck a pedestrian.
- **Compulsions:** Repetitive behaviors (hand washing, praying, or repetition of words) that an individual feels compelled to perform.

STRESS REACTIONS

Part of the larger grouping of anxiety disorders. Separated here because all three are related, i.e., they result from exposure to a certain stressor and differ in terms of their duration.

Post-Traumatic Stress Disorder

Occurs after a traumatic event in which the individual experienced or witnessed threatened death or serious injury to themselves or others. Symptoms include avoidant behaviors, feelings of emotional numbness, hypervigilance, insomnia, and angry outbursts lasting at least 1 month. A key component is re-experiencing the event (in a variety of ways).

- Flashbacks
- Dreams or nightmares

- Recurrent intrusive thoughts of the event
- Distress when exposed to a similar event

Acute Stress Disorder

Symptoms are similar to those of PTSD. Lasts > 2 days and < 4 weeks. Must occur within 4 weeks of the traumatic event.

Adjustment Disorder

Occurs following exposure to a psychological stressor (e.g., moving, divorce, or family death). Resultant emotional symptoms (depression and anxiety) cause significant functional impairment. Lasts < 6 months.

SOMATOFORM DISORDERS

Defined as physical symptoms that seem as if they are part of a general medical condition; however, no general medical condition, other mental disorder, or substance is present. Psychological conflicts may be manifest as physical problems or complaints. The patient has no conscious awareness of the motivation behind the complaints, and they are not intentionally produced. In contrast to factitious disorder and malingering, secondary gain is not responsible for symptoms.

Somatization Disorder

Numerous physical complaints over several years beginning earlier than age 30 resulting in impairment of function and treatment-seeking behavior. No evidence for symptoms can be found on clinical investigation.

- **Symptoms:** Four pain symptoms, two GI symptoms, one sexual symptom, and one pseudoneurological symptom.
- Symptoms not intentionally produced or feigned.

Conversion Disorder

At least one sensory or motor symptom suggesting a neurological problem. No cause can be found after clinical investigation.

- **Example:** A young woman complains of blindness after witnessing a murder even though she drove herself to the doctor's office.
- Symptoms are not intentionally produced or feigned.

Hypochondriasis

Preoccupation with the fear of having a serious disease based on misrepresentation of body symptoms. Preoccupation persists despite adequate medical evaluation and reassurance. Symptoms cause significant distress. Lasts < 6 months.

Body Dysmorphic Disorder

Perceived defect in appearance. Concern is markedly excessive even in the presence of slight physical defects and causes significant impairment.

- **Example:** A young female seeks plastic surgery for the fourth time because "her nose is huge and bumpy," despite a normal appearance.

FACTITIOUS DISORDER AND MALINGERING

While patients with the somatoform disorders have an unconscious drive to their disorders, patients with factitious disorder and malingering have conscious motivation of secondary gain. Secondary gain may include assuming the sick role, obtaining monetary benefit, or avoiding jail or military service.

Factitious Disorder

Intentional production of physical signs or symptoms in order to assume the sick role. There is no external motivation (economic gain or avoidance of legal liability).

Malingering

Intentional production of false or exaggerated physical symptoms associated with external gain (e.g., financial gain, avoiding military duty, or avoiding criminal prosecution).

DISSOCIATIVE DISORDERS

All involve temporary alterations in identity, memory, or consciousness and are recognized as separate entities based on what information is affected. With amnesia, it may be events or information, while with fugue states the emphasis is loss of personal identity followed by travel away from one's home. Dissociative identity disorder is the condition classically known as "multiple personalities."

Dissociative Amnesia

At least one episode of inability to recall important personal information following stress or traumatic exposure. Failed recall is too extensive to be attributable to forgetfulness.

Dissociative Fugue

Sudden, unexpected travel away from home and assumption of a new identity with inability to recall one's past.

- **Example:** A 45-year-old married female teacher disappears from home only to reappear in a new town as a waitress and remarry. When her first husband appears, she does not know who he is.

Dissociative Identity Disorder

Formerly known as "multiple personality disorder." The presence of two or more distinct personality states, each with its own distinct way of relating to the environment and itself.

Depersonalization Disorder

Persistent or recurrent experiences of feeling detached from one's body or mental processes.

SUICIDE

Recognizing risk factors and key points are high-yield topics. Suicide is the eighth leading cause of death for men. Men are four times as likely to die from a suicide attempt as women, while women are three times as likely as

men to attempt suicide. According to the CDC, just over 30,000 people died of suicide in 2001.

- **Risk factors:** Age (teens and the elderly), depression, previous attempts, drug or alcohol use, medical illness, being single, lack of social support, having a suicide plan.
- **Key points:** Attempts: Female > male. Completions: Male > female.

SUBSTANCE ABUSE

Maladaptive pattern of substance use leading to functional impairment. Symptoms must have never met the definition of substance dependence (see Table 7-25):

- Failure to fulfill home or work obligations.
- Repeated use in hazardous situations (e.g., drunk driving).
- Recurrent associated legal problems.
- Continued use despite social or interpersonal problems related to substance use.

SUBSTANCE DEPENDENCE

Maladaptive pattern of substance use leading to functional impairment as well as **tolerance, withdrawal, desire or inability to cut down**, significant amount of time spent obtaining the substance, reduced social or occupational activity due to substance use, or continued use despite deleterious health effects.

- **Tolerance:** Need for increased amounts of substance to achieve the same effect, or diminished effect following use of the same amount of substance.
- **Withdrawal:** Characteristic withdrawal symptoms of a particular substance.

DELIRIUM

Acute disturbance of consciousness with change in cognition, reduced ability to focus attention, or perceptual disturbance. The course tends to fluctuate throughout the day. Must not be accounted for by pre-existing dementia.

- **Delirium versus dementia:** Delirium is more acute in onset and follows a waxing and waning course.
- **Common causes:** Metabolic causes, electrolyte disturbances, diabetes, thyroid disease, dehydration. Pharmacologic therapy is a frequent cause, particularly anticholinergics, sedatives, antidepressants, NSAIDs, steroids, antibiotics, cimetidine, L-dopa, and several others. Other causes include infection, fever, hypoxia, and head trauma.

DEMENTIA

Development of memory impairment along with multiple other cognitive deficits, such as language disturbance, apraxia, agnosia, or disturbance in executive functioning. Deficits cause significant impairment in functioning. Must not be related to other medical or CNS disorders (see Table 7-26).

- **Apraxia:** Defined as the inability to make a voluntary movement in spite of normal muscle function. An example would be asking a patient to demonstrate how they brush their hair or throw a baseball, and they cannot despite normal strength.

TABLE 7-25. Drugs of Abuse and Their Effects

Drug	Intoxication	Withdrawal
Alcohol	Disinhibition, emotional lability, slurred speech, ataxia, coma, blackouts.	Tremor, tachycardia, hypertension, malaise, nausea, seizures, delirium tremens (life-threatening), tremulousness, agitation, hallucinations.
Opioids	CNS depression, nausea and vomiting, constipation, pupillary constriction, seizures.	Anxiety, insomnia, anorexia, sweating, dilated pupils, piloerection, fever, rhinorrhea, nausea, stomach cramps, diarrhea, yawning.
Amphetamines	Agitation, impaired judgment, pupillary dilation, hypertension, tachycardia, euphoria, prolonged wakefulness and attention, arrhythmias, delusions, hallucinations, fever.	Post-use "crash" including depression, lethargy, headache, stomach cramps, hunger, hypersomnolence.
Cocaine	Euphoria, agitation, impaired judgment, tachycardia, pupillary dilation, hypertension, hallucinations, paranoia, angina, sudden cardiac death.	Post-use "crash" including depression and suicidality, hypersomnolence, fatigue, malaise, craving.
Phencyclidine (PCP)	Belligerence, impulsiveness, fever, agitation, nystagmus, tachycardia, ataxia, homicidality, psychosis, delirium.	Recurrence of intoxication symptoms due to reabsorption in the GI tract; sudden onset of severe, random, homicidal violence.
Lysergic acid diethylamide (LSD)	Anxiety, depression, delusions, hallucinations, flashbacks, pupil dilation.	No recognized withdrawal symptoms.
Marijuana	Euphoria, anxiety, paranoia, slowed time perception, poor judgment, social withdrawal, increased appetite, dry mouth, hallucinations.	No recognized withdrawal symptoms.
Barbiturates	Respiratory depression (more profound than with benzodiazepines).	Anxiety, seizures, delirium, cardiovascular collapse.
Benzodiazepines	Amnesia, ataxia, somnolence, minor respiratory depression. Additive with alcohol.	Rebound anxiety, seizures, tremor, insomnia.
Caffeine	Restlessness, insomnia, diuresis, muscle twitching, arrhythmias.	Headache, lethargy, depression, weight gain.
Nicotine	Restlessness, insomnia, anxiety, arrhythmias.	Irritability, headache, anxiety, weight gain, craving.

- **Agnosia:** Loss of the ability to interpret stimuli and usually classified according to the type of senses that are affected. This may include not recognizing faces of people familiar to the patient, or not recognizing an object (e.g., coin or paper clip) placed in the hand while their eyes are closed.
- **Types:** Alzheimer's, vascular (multi-infarct), and frontotemporal, among others.

TABLE 7-26. Types of Dementia and Their Characteristics

Type of Dementia	Points to Remember
Alzheimer's disease	Associated with diffuse cortical atrophy and cognitive deficits along with acetylcholine (ACh) deficiency.
Vascular (multi-infarct) dementia	Chronic stepwise cognitive decline in patient with long-standing uncontrolled hypertension.
Frontotemporal dementia	Chronic dementia that typically presents with language deficits and behavioral changes.
Alcohol-related dementia	Dementia in the setting of chronic alcohol abuse. This is one of the few dementias that may be reversible.
AIDS-related dementia	Many HIV and AIDS patients may go on to develop dementia as an effect of the virus on their CNS.
Creutzfeldt-Jakob disease (CJD)	Dementia accompanied by ataxia and other signs of neurodegenerative disease in a setting of prion disease.
Parkinson's disease	An Alzheimer's type dementia is usually associated in most patients with Parkinson's disease (*pill-rolling tremor, masked facies,* shuffling gait).

EATING DISORDERS

Involve an unhealthy body image by the patient and a desire to be thin. Both are related to control issues and obsessive-compulsive traits. On a test, anorexia will involve failure to maintain normal weight for height along with menstrual changes, while bulimia will be more associated with binging and purging behavior.

Anorexia Nervosa

Refusal to maintain weight ≥ 85% of ideal body weight. Seen frequently in adolescent females with "type A" personalities.

- **Amenorrhea:** Must have absence of menstrual periods for 3 months for this diagnosis (in females).
- **Associations:** Intense fear of becoming fat, poor body image despite being thin, and depression.

Bulimia Nervosa

Recurrent episodes of binge-purge behavior. Individuals will eat a great deal of food with a sense of lack of control over eating, followed by compensatory purging behavior (self-induced vomiting, laxative or diuretic abuse, fasting, or excessive exercise). Episodes occur ≥ 2/week for 3 months.

- **Associations:** Parotitis, enamel erosion, electrolyte disturbance, and dorsal hand calluses (from induction of vomiting).

PERVASIVE DEVELOPMENTAL DISORDERS

All are characterized by pervasive and severe impairment in several areas to include social and communicative skills, as well as the presence of stereotyped movements and behaviors. However, the similarities end there. Some, like Rett's disorder and childhood disintegrative disorder, involve totally normal development until a certain time, followed by growth abnormalities and loss of previously learned skills.

Autistic Disorder

Present in childhood with impaired social interactions and **communication deficits**. Do not form relationships with others. Have poor eye contact. May also be adherent to routines and can display stereotyped movements/behaviors.

Asperger's Disorder

Similar to autism but less severe. Lacks language/communication deficits.

Rett's Syndrome

Only affects **females** (affected males believed to die in utero). Development is normal until 5 months of age, with a subsequent deterioration to include deceleration of head growth and loss of previously acquired motor skills.

Childhood Disintegrative Disorder

Apparently normal development for the first 2 years of life with subsequent deterioration including loss of motor and communicative skills.

DISRUPTIVE BEHAVIOR DISORDERS

Group of disorders of children and adolescents that consist of behavior that violates social norms, is disruptive, and may be illegal. Disorders occur along a spectrum. Remember that oppositional defiant disorder is more defiance and verbal rebellion toward authority figures, while conduct disorder is usually destructive behavior that harms others or property.

Attention Deficit/Hyperactivity Disorder

Symptoms must begin prior to age 7 and be present in two or more social situations (i.e., at school and at home). There are two subtypes.

- **Inattentive:** Difficulty sustaining attention, poor attention to detail in homework, and easily distracted.
- **Hyperactive/Impulsive:** Fidgeting, difficulty remaining seated in class, excessive talking, and difficulty awaiting one's turn.

Oppositional Defiant Disorder

Hostile and defiant behavior lasting >6 months. Child or teenager is argumentative with authority figures and refuses to obey rules. Absence of criminal behavior (compared with conduct disorder).

Conduct Disorder

Pattern of behavior in which social norms and rights of others are violated. May display aggression to other people or animals, destruction of property, theft, and rule violations. Individuals may go on to develop antisocial personality disorder.

TIC DISORDERS

Can be verbal, motor, or both. Remember that Tourette's syndrome has both motor and vocal components, while transient and chronic tic disorders have one or the other. Note that the only difference between transient tic disorder and chronic tic disorder is the time course.

Tourette's Syndrome

Presence of both motor and vocal tics (not necessarily concurrently) several times a day over the course of 1 year, with no tic-free period of > 3 months. Onset before age 18.

Transient Tic Disorder

Motor or vocal tics that occur several times a day for at least 4 weeks but less than 1 year. Onset before age 18.

Chronic Motor or Vocal Tic Disorder

Single motor or vocal tics (but not both) occurring for ≥ 1 year without a tic-free period of more than 3 months. Onset before age 18.

ELIMINATION DISORDERS

Elimination disorders involve children that are beyond the age typical of successful toilet training, having inappropriate passage of urine or feces. Causes may be medical and/or psychiatric.

Enuresis

Repeated urination in bed or clothes at least twice a week for 3 months. Child must be at least 5 years of age.

Encopresis

Repeated defecation in inappropriate places at least once a month for at least 3 months. Child must be at least 4 years of age.

OTHER CHILDHOOD AND EARLY-ONSET DISORDERS

Mental Retardation

Significant below-average intellectual and adaptive functioning with the onset before age 18. Graded into mild, moderate, severe, and profound, based on IQ scores.

Separation Anxiety Disorder

Inappropriate and excessive anxiety about being away from individuals the patient has close relationships with (e.g., mother, father, or grandparent). Manifests as excessive worry, distress when separated, or reluctance to engage in events that separates the patient from the individual (going to school). May lead to nightmares or physical complaints (upset stomach).

Reactive Attachment Disorder

Formation of socially inappropriate attachments or relatedness beginning before 5 years of age. The child either makes no significant or obvious social relationships, or the child may develop diffuse emotional attachments to

many individuals. Occurs when basic emotional needs of the child have not been met (frequent change of primary caregiver).

PERSONALITY DISORDERS

Occur when personality traits become inflexible and maladaptive causing impairment in social or occupational functioning. Patients with PDs lack insight into the problem. Usually diagnosed in adulthood.

- **Personality traits:** Persistent pattern of relating to or interaction with the environment or others.
- **"Clusters":** Personality disorders are categorized by overarching characteristics into three clusters: A (the "weird"), B (the "wild"), and C (the "worried").

PERSONALITY DISORDER: CLUSTER A

The "weird." Odd or eccentric. Cannot develop meaningful personal relationships. No psychosis, but genetic association with schizophrenia.

Schizotypal PD

Awkwardness in interpersonal functioning, odd beliefs, and "magical" thinking (superstitiousness, bizarre fantasies). Eccentric appearance. Acute discomfort with and reduced capacity for interpersonal relationships.

Schizoid PD

These individuals avoid personal relationships. Also have restricted range of emotional expression. These individuals do not desire close relationships, and choose solitary activities. No magical thinking as with schizotypal PD.

Paranoid PD

Pervasive distrust and suspiciousness of others. Preoccupation with perceived lack of loyalty and trustworthiness of friends and significant others. Bears grudges and constantly finds hidden meanings in otherwise harmless comments.

PERSONALITY DISORDERS: CLUSTER B

The "wild." Dramatic, emotional, or erratic. Strong associations with substance abuse and mood disorders.

Antisocial PD

Disregard for and violation of the rights of others. Significant criminal behavior, as well as significant criminal record without remorse for actions. Must be at least 18 years of age, as well as have a history of conduct disorder prior to age 15. Males > females.

Borderline PD

Pervasive pattern of unstable relationships, poor self-image, labile mood, and impulsivity. Recurrent self-injurious behavior (i.e., "cutting"); may even be suicidal. May engage in "splitting" (relationships are all good or all bad). Frequent outbursts and difficulty controlling anger. Female > male.

Histrionic PD

Excessively emotional; seeks attention. Desires to constantly be the center of attention, and may be sexually provocative or inappropriate. Uses physical appearance to draw attention to self. Often thinks relationships are more intimate than they are in reality.

Narcissistic PD

Pervasive pattern of grandiosity, increased sense of self, need for admiration, and lack of empathy for others. Believes that they are "special" and think they are entitled to special treatment, as well as want to associate with the "best of the best" (i.e., may want to be treated by the chief of the medical department rather than a resident).

PERSONALITY DISORDERS: CLUSTER C

The "worried": Anxious or fearful. Genetic association with anxiety disorders.

Avoidant PD

Displays social inhibition and feelings of inadequacy; timid and sensitive to rejection. Avoid interpersonal relationships for fear of rejection. Unlike schizoid PD, desires personal relationships, although may not have many.

Obsessive-Compulsive PD

Displays preoccupation with orderliness, perfectionism, and control, at the expense of flexibility and efficiency. Perfectionism may interfere with task completion, as well as social interactions. Prone to hoarding worn-out or worthless objects, and particularly frugal or miserly with finances.

Dependent PD

Needs to be taken care of that leads to submissive and clingy behavior as well as fear of separation. Difficulty making decisions, as well as disagreeing with others. This may manifest as the wife who is physically abused by her husband, but stays in the relationship nonetheless, possibly even placing the blame for the abuse on herself.

NOTES

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Renal

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Embryology

RENAL DEVELOPMENT

The urinary system is derived from the **intermediate mesoderm** on the posterior wall of the abdominal cavity (see Table 8-1). It forms three kidney systems, namely, the pronephros, mesonephros, and metanephros:

- **Pronephros:** Forms first, is nonfunctional, and disappears by end of fourth week.
- **Mesonephros:** Forms after regression of the pronephros and forms the mesonephric (**wolffian**) duct.
  - **Wolffian duct:** Paired organ that connects the primitive **mesonephros** to the **cloaca**. The presence or absence of **testosterone** in utero determines which adult analogues it will form.
- **Metanephros:** Forms the definitive kidney.

Potter's Sequence

Potter's sequence develops as a result of malformation of the **ureteric bud**, which results in **bilateral renal agenesis**. During normal fetal development, the fetus continuously swallows amniotic fluid, which is reabsorbed by the GI tract and then reintroduced into the amniotic cavity by the kidneys via urination. Fetuses affected with this condition are unable to eliminate the swallowed fluid, which results in **oligohydramnios** (decreased amniotic fluid).

PRESENTATION

The deformities found in Potter's sequence can be divided into three groups.

- **Limb deformities:** Clubfoot, flipper hands, hyperextensible joints, and compressed thorax.
- **Facial deformities:** Sloping forehead, flattened nose, recessed chin, and low floppy ears. The fetus cannot float in the amniotic sac due to the decreased volume of amniotic fluid, so limb and facial deformities result from compression of the fetus against the walls of amniotic sac throughout development.

CLINICAL CORRELATION

Men without testosterone may have normal external male genitalia. **Wolffian duct** system regression causes **delayed puberty** in men.

KEY FACT

Allantois → urachus → medi**an** umbilical ligament (not to be confused with the medi**al** umbilical ligament, which is the remnant of the umbilical arteries).

Following a failure of obliteration of the allantois, a **patent urachus** can result in an **urachal fistula** at birth.

Urogenital sinus → urinary bladder and urethra.

TABLE 8-1. Renal Development

Portion of Kidney	Embryonic Origin	Adult Structures
Excretory system	Derived from primary ***metanephric mesoderm.***	Glomerulus. Bowman's capsule. Loop of Henle. Distal collecting tubule. Collecting system.
Collecting ducts	Outgrowth of the ***mesonephric duct*** joins the metanephros to form the **ureteric bud.**	Major/minor calyces. Renal pelvis. Ureters (splitting of the ureteric bud can result in double ureters).

- **Pulmonary hypoplasia:** Fetal lungs mature through swallowing of amnion which allows the lungs to expand; thus decreased amnion causes decreased expansion of the lungs.

MNEMONIC

Babies with **Potter's** can't **Pee** in utero.

PROGNOSIS

Incompatible with neonatal life.

Pelvic Kidney

During development, the embryologic kidneys ascend from the pelvis to their adult position along the posterior abdominal wall. The kidneys must pass under the **umbilical arteries** in this process. If a kidney is unable to pass beneath an umbilical artery, it will remain in the pelvis. Incidence is 1 in 900 births.

PRESENTATION

Obstructive **hydronephrosis** and **vesicoureteric** reflux are seen in association with renal ectopy. Affected patients may present with pain or infection related to these conditions (e.g., pyelonephritis and renal stones). Many cases are clinically silent and are often discovered incidentally.

DIAGNOSIS

Found incidentally on imaging for symptoms of associated anomalies.

TREATMENT

Treatment is generally surgical although surgery can be challenging due to the aberrant anatomy.

PROGNOSIS

Prognosis is related to the underlying urologic disease.

Horseshoe Kidney

While ascending from their position in the pelvis under the umbilical arteries, the kidneys are sometimes pushed close together, causing the lower poles to fuse (**fusion anomaly**). The resultant horseshoe-shaped kidney will continue to ascend until it is trapped under the **inferior mesenteric artery** (see Figure 8-1). It is rare in females and if found should prompt work-up for Turner's syndrome (7% of Turner's patients have this defect).

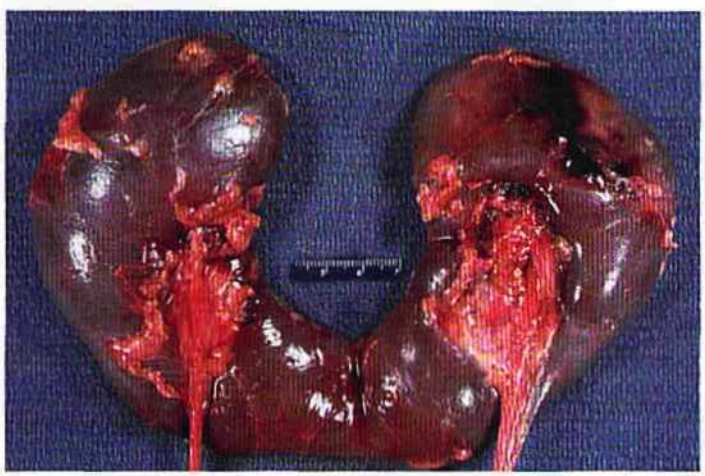


FIGURE 8-1. Horseshoe kidney. (Courtesy of PEIR Digital Library [http://peir.net].)

Presentation

Ninety percent are asymptomatic and found incidentally. Most common presentation is **urinary tract infection** (UTI) followed by symptoms of obstruction, hematuria, or abdominal pain. Predisposes to **nephrolithiasis**.

Diagnosis

Intravenous pyelogram (IVP) shows diagnostic features of rotated calyces, but does not demonstrate the isthmus. A dimercaptosuccinic acid (DMSA) scan will show the isthmus.

Treatment

Usually not necessary unless warranted by symptoms. The renal isthmus can be surgically divided.

Anatomy

POSTERIOR ABDOMINAL WALL

The posterior abdominal wall is supported by several large muscles attached to the bony thorax, vertebral column, and pelvic bones. It is atop these muscles and their skeletal insertions that the retroperitoneal structures are found. Table 8-2 details these muscles and their innervation, blood supply, and actions.

RETROPERITONEAL STRUCTURES

Much of the urinary system is comprised of retroperitoneal organs. (Other retroperitoneal organs include the pancreas [except the tail], duodenum [second, third, and fourth parts], ascending colon, descending colon, aorta, IVC, rectum, and adrenal glands [see Figures 8-2 and 8-3]).

TABLE 8-2. Muscles of the Posterior Abdominal Wall

	Origin/Insertion	Innervation	Blood Supply	Actions
Psoas major	Vertebral column (T12–L5) to the lesser trochanter of the femur.	Ventral rami of L1–3	Muscular branches of the medial femoral circumflex artery.	Flexes thigh and trunk and laterally rotates the hip.
Psoas minor	Vetebral column (T12–L1) to the pectineal line.	Anterior rami of lumbar nerves L1–L2		With the psoas major, flexes the trunk at the hip and stabilizes the thigh.
Iliacus	Iliac fossa to the lesser trochanter of the femur.	Femoral nerve (L3–L4)	Muscular branches of the medial femoral circumflex artery.	Powerful hip flexor and lateral rotation.
Quadratus lumborum	Transverse processes of L3–L5 to the lower border of the 12th rib.	Ventral branches of T12 and L1–L4		Extends and laterally flexes vertebral column.

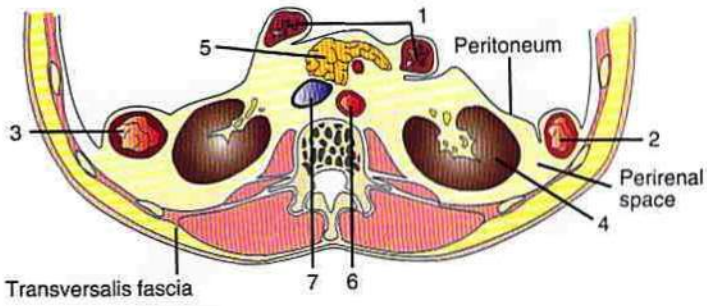


FIGURE 8-2. Schematic representation of the retroperitoneum. 1 = duodenum (second, third, and fourth parts); 2 = descending colon; 3 = ascending colon; 4 = kidney and ureters; 5 = pancreas (except the tail); 6 = aorta; 7 = inferior vena cava. The adrenal glands and rectum are not shown in this diagram.

- **Kidneys:** Located at the level of T12–L3 on the left and slightly lower on the right due to the liver, these are embedded in **Gerota's fascia** (loose connective tissue).
- **Ureters:** Descend from their origin at the renal pelvis along the psoas muscle, cross the bifurcation of the common iliac artery, pass **under** the uterine artery and vas deferens, and then join with the bladder in its posterior–inferior portion.
- **Bladder:** Situated beneath the peritoneum within the bony pelvis.

MNEMONIC

Water **(ureters)** under the bridge **(artery and vas deferens).**

Kidney

The kidney (see Figure 8-4) is a retroperitoneal organ situated on the mediolateral aspect of the posterior abdominal wall. The point of maximal concavity (hilum) is the site where the renal arteries and veins, as well as the ureters, adjoin the kidney.

- **Arterial supply:** Renal arteries are branches of the abdominal aorta.
- **Venous return:** Renal veins drain into the IVC.
- **Left renal vein:** Also drains blood from the left gonad and is longer than the right renal vein (must cross the aorta to join the IVC).

KEY FACT

Right gonadal vein drains into the **inferior vena cava.**
Left gonadal vein drains into the ***left renal vein.***

Lymphatic drainage is to the lumbar nodes, nerve supply is via the thoracic splanchnic nerves.

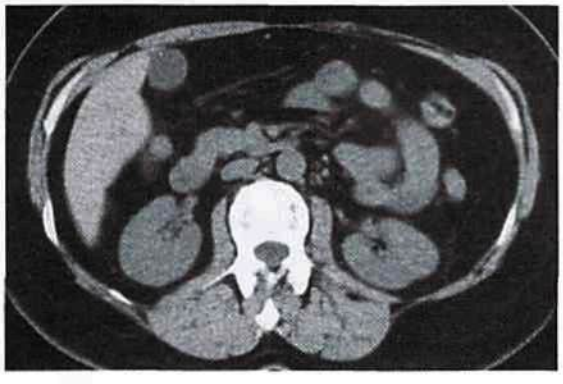


FIGURE 8-3. Normal noncontrast CT image of the kidneys. Note the smooth contour and relative symmetry of the kidneys and their sharp interface with the perirenal fat. (Reproduced, with permission, from Chen MYM, Pope TL, Ott DJ. *Basic Radiology.* New York: McGraw-Hill, 2004: 230.)

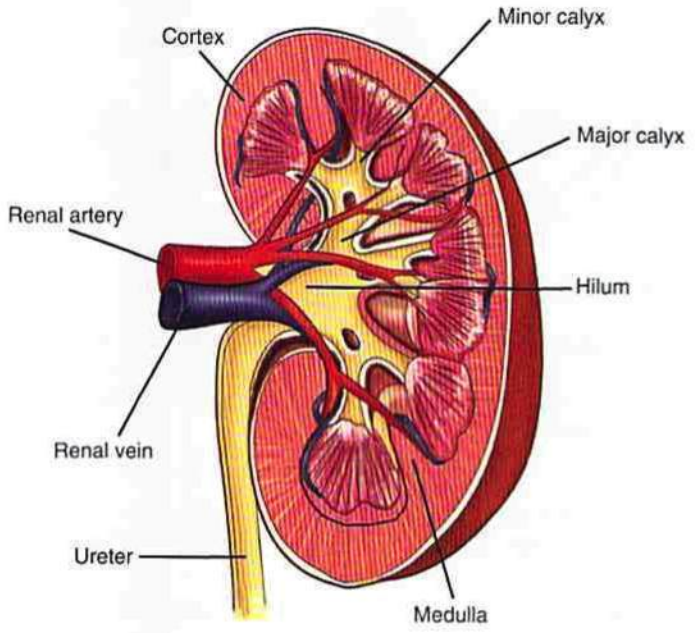


FIGURE 8-4. Gross anatomy of the kidney section.

The kidney itself is covered in a cortex of fibrous tissue. Beneath this cortex, the medulla and the functional components of the kidney are found. The medulla is comprised of the early portions of the urinary collecting system (the direction of urinary drainage):

- Renal pyramids
- Renal papillae
- Minor calyces
- Major calyces

The major calyces join to form the renal pelvis, a dilatation of the collection system before the take off of the ureters.

Ureters

The ureters course distally through the retroperitoneum before crossing the pelvic brim near (and anterior to) the bifurcation of the common iliac artery into the internal and external iliac arteries. The **ureters** pass **under** the **uterine artery** and the **ductus deferens**. However, they pass **over** the **common iliac arteries.** They cross the pelvic brim just anterior to the origin of the common iliac arteries.

Bladder

The ureters join the bladder at its posterior–inferior portion, forming two points of the urinary trigone. The bladder is an expandable and collapsible organ comprised of several layers.

Urethra

The urethra is lined by **transitional epithelium** as it exits the bladder. It then becomes **stratified columnar** followed by **stratified squamous** as it nears the meatus. The urethra differs in males and females:

Male Urethra

Four anatomical divisions:

- **Prostatic:** Passes through the prostate gland.
- **Membranous:** Surrounded by striated muscle, which forms the voluntary external urethral sphincter (weakness produces urinary incontinence).
- **Bulbous.**
- **Pendulous:** Surrounded by **Littre's glands.**

CLINICAL CORRELATION

As men age, the prostate expands (benign prostatic hypertrophy), and the urethra becomes compressed, leading to possible urinary retention.

Female Urethra

Much **shorter** than the male urethra, which predisposes women to an **increased risk of UTIs.** It is lined by **stratified squamous** and **pseudostratified columnar epithelium.** At its mid-portion, it is surrounded by the striated muscle of the voluntary external urethral sphincter. The female urethra is also surrounded by **Littre's glands.**

Histology

An overview of the histological characteristics of the respective structures that form the renal system is provided in Table 8-3.

NEPHRON

The nephron is the primary functional unit of the kidney. It is the body's filtration system, as it removes substances from the blood and creates urine. It is composed of the **renal corpuscle** and the **tubular system** (see Figure 8-5).

TABLE 8-3. Histological Characteristics of the Respective Renal Organs

Structure	Histology
Glomerulus	Fenestrated endothelium.
Bowman's capsule	Epithelium with two layers: visceral layer and parietal layer.
Proximal convoluted tubule (PCT)	Simple cuboidal epithelium with brush border.
Loop of Henle	Thick descending loop; thin descending loop; thin ascending loop; thick ascending loop.
Distal convoluted tubule (DCT)	Simple cuboidal epithelium without brush border.
Collecting tubules	Simple cuboidal epithelium.
Collecting ducts	Columnar epithelium.
Renal calyces	Transitional epithelium.
Renal pelvis	Transitional epithelium.
Ureters	Transitional epithelium.

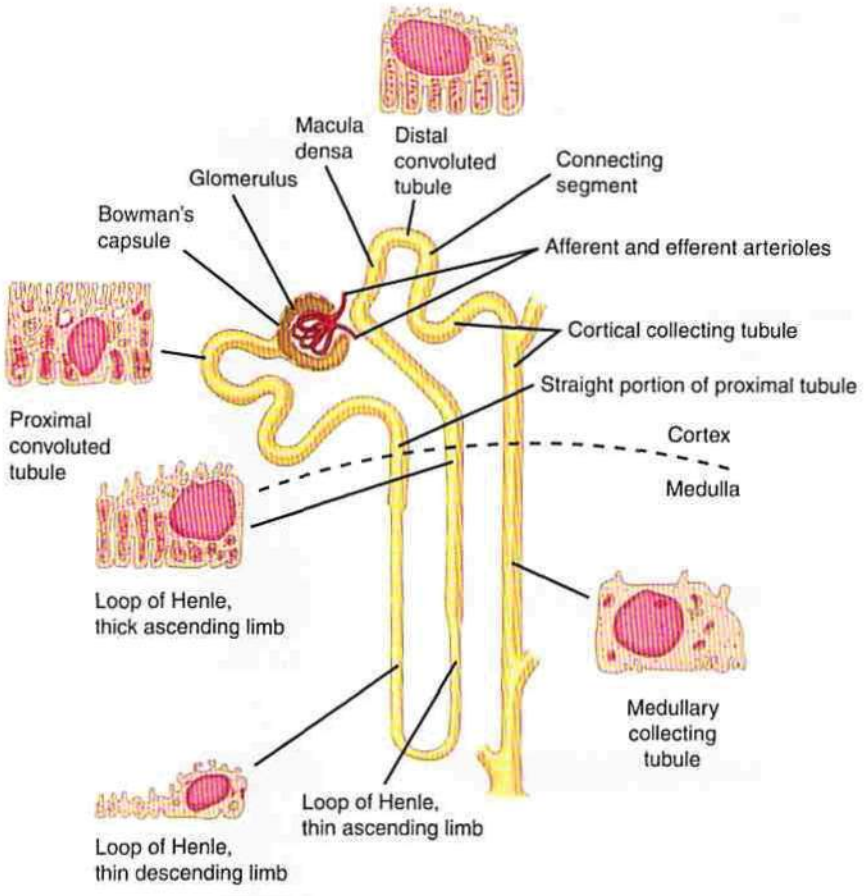


FIGURE 8-5. Major anatomic divisions of the nephron. (Modified, with permission, from Morgan GE, Mikhail MS, Murray MJ. *Clinical Anesthesiology*, 4th ed. New York: McGraw-Hill, 2006, as modified from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005: 700.)

KEY FACT

Glomerulus + Bowman's capsule = Renal corpuscle.

CLINICAL CORRELATION

Damage to this filtration barrier allows larger molecules, including proteins, to cross the filter, resulting in **proteinuria.**

FLASH FORWARD

Proteinuria is a cardinal symptom of the **nephrotic syndrome.**

Renal Corpuscle

The renal corpuscle is the primary filtering component of the nephron and is composed of two distinctive functional units: the glomerulus and Bowman's capsule.

Glomerulus

A collection of dilated capillaries with fenestrated endothelium, which emerge from the afferent arteriole and drain into the efferent arteriole.

Bowman's Capsule

Double-walled epithelial capsule (see Figure 8-6), that encloses the glomerulus. Bowman's capsule is the site of blood filtration and consists of two functional layers, visceral and parietal, divided by the urinary space.

- The **visceral layer** is a specialized outer lining on glomerular capillaries that filters the blood in these capillaries, creating a filtrate in the urinary space. The specialized lining includes:
  - Podocytes, which rest on the basement membrane (see Figure 8-7)
  - Primary processes
  - Foot processes
- The **parietal layer** forms the other covering of the renal corpuscle, and is lined by a simple squamous epithelium supported by a basal lamina. This layer is continuous with the proximal convoluted tubule (PCT).

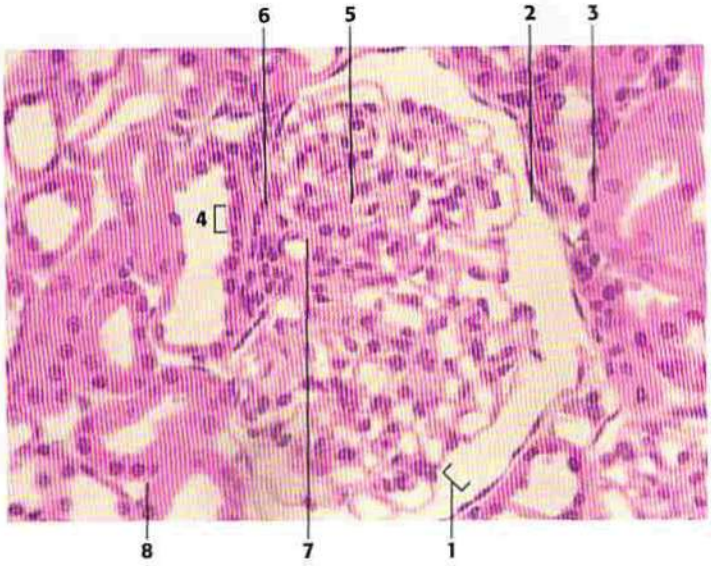


FIGURE 8-6. Components of the renal corpuscle (H&E, normal kidney). 1 = Bowman's space; 2 = Bowman's capsule, visceral layer; 3 = Bowman's capsule, parietal layer; 4 = macula densa; 5 = intraglomerular mesangial cell; 6 = extraglomerular mesangial cell; 7 = arteriole; 8 = capillary, peritubular; 9 = capillary, glomerular. (Courtesy of Uniformed Services University of the Health Sciences.)

- The **urinary space** is found between the visceral and parietal layers. At this point, filtrate collects after passing through the fenestrated capillary endothelium of the glomerulus and the visceral layer of Bowman's capsule.

Tubular System

The renal tubular system is divided into several functional units: **PCT, loop of Henle, distal convoluted tubule (DCT), collecting tubules,** and **collecting ducts.**

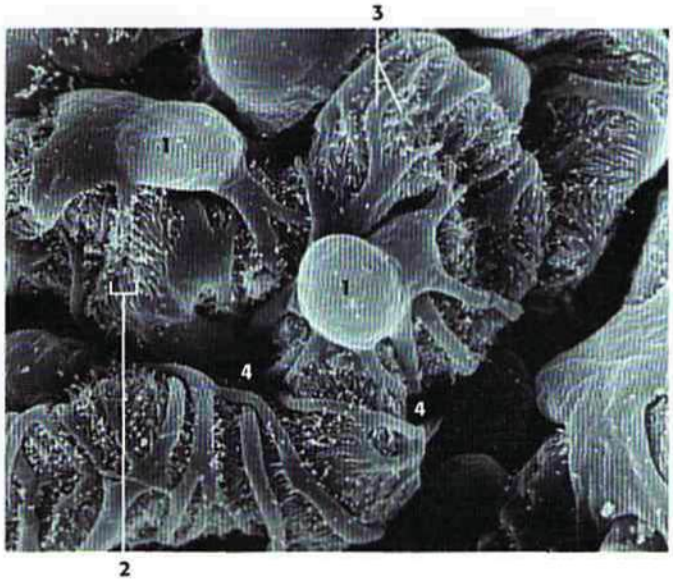


FIGURE 8-7. Electron photomicrograph of podocytes. 1 = Podocyte cell bodies; 2 = interdigitating pedicles; 3 = trabeculae; 4 = Bowman's space. (Courtesy of Uniformed Services University of the Health Sciences.)

Proximal Convoluted Tubule

The lumen is lined with **simple cuboidal epithelium** containing a **microvillous brush border** (see Figure 8-8). Extensive interdigitations between the lateral borders of the cells prevent the escape of fluid and molecules from the tubule.

Loop of Henle

A specialized system that handles absorption and secretion of electrolytes, small molecules, and water. It consists of a **thick descending loop**, a **thin descending loop**, a **thin ascending loop**, and a **thick ascending loop.**

Distal Convoluted Tubule

Lined with **simple cuboidal epithelium.** However, it **does not** have a **brush border**, distinguishing it from the PCT (see Figures 8-9 and 8-10).

Collecting Tubules

These units are lined with **simple cuboidal** epithelium. They transport the urine from the **functional part** of the **nephron** towards the **kidney's hilum.**

Collecting Ducts

Lined with **columnar** epithelium.

Cortical and Juxtamedullary Nephrons

Most of the kidney's nephrons are located in the renal cortex. However, the glomerulus of some nephrons is located near the junction of the kidney's cortex and medulla. These nephrons are referred to as **juxtamedullary nephrons.**

- **Juxtamedullary nephrons** are central in the filtration, absorption, and secretion of urine. Via exceptionally long loops of Henle, they establish the hypertonic gradient in the kidney which regulates the production of concentrated urine. The loops **extend deep into the medulla,** and consist

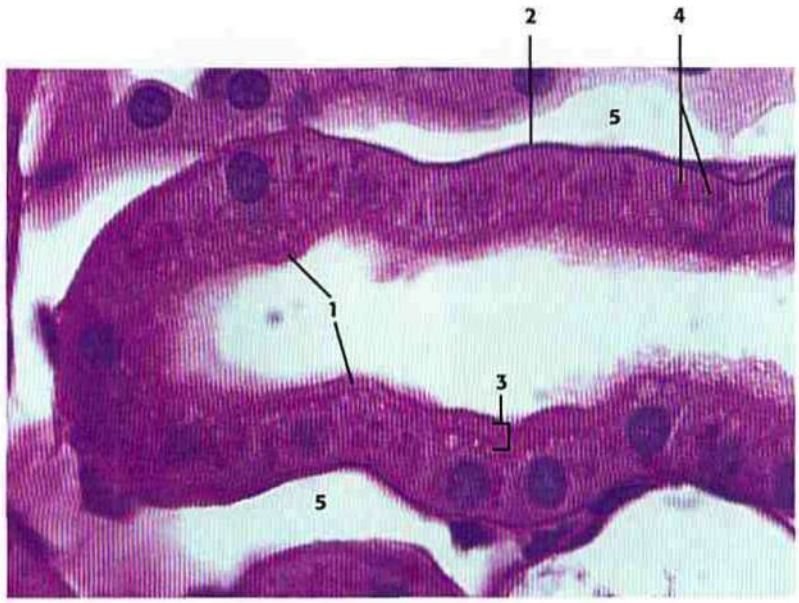


FIGURE 8-8. Structure of the proximal convoluted tubule. 1 = Endocytic vacuoles; 2 = basement membrane; 3 = brush border; 4 = lysosomes; 5 = peritubular capillaries. (Courtesy of Uniformed Services University of the Health Sciences.)

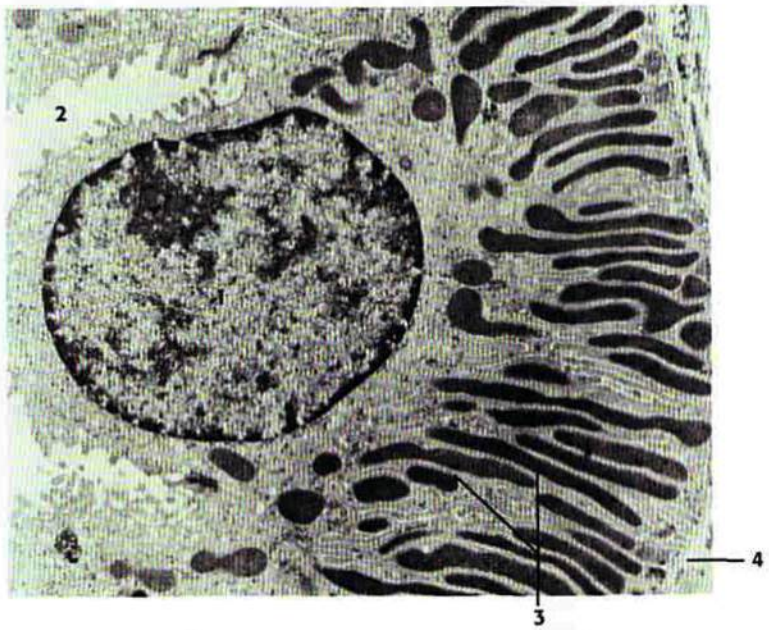


FIGURE 8-9. Electron photomicrograph of the distal convoluted tubule. 1 = Nucleus; 2 = lumen; 3 = basal mitochondria in compartments (formed by interdigitating membranes); 4 = basal lamina. (Courtesy of Uniformed Services University of the Health Sciences.)

of a short thick descending limb, a long thin descending limb, a long thin ascending limb, and a short thick ascending limb.

- **Cortical nephrons** have a short thin descending limb and do not have a thin ascending limb.

JUXTAGLOMERULAR APPARATUS

The juxtaglomerular apparatus (JGA) consists of **macula densa** cells found in the proximal portion of the distal tubule, and **juxtaglomerular cells** found

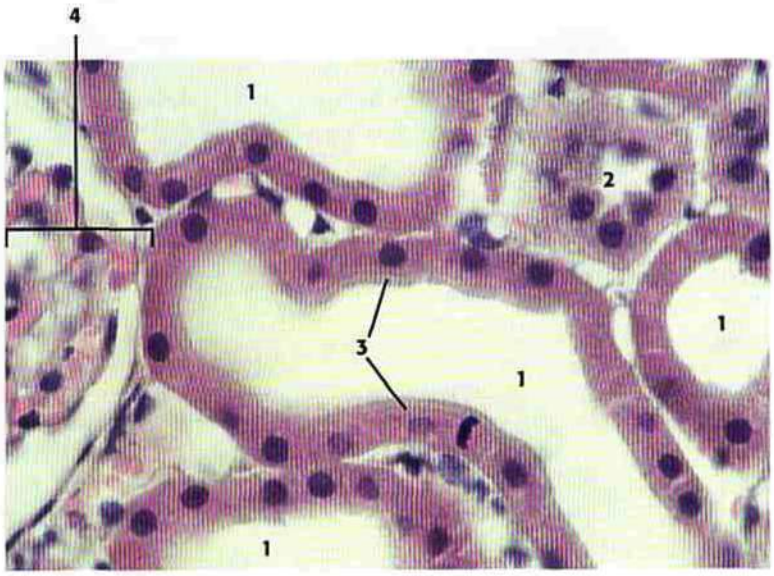


FIGURE 8-10. Proximal and distal convoluted tubules. 1 = Proximal convoluted tubules; 2 = distal convoluted tubules; 3 = brush border; 4 = renal capsule. (Courtesy of Uniformed Services University of the Health Sciences.)

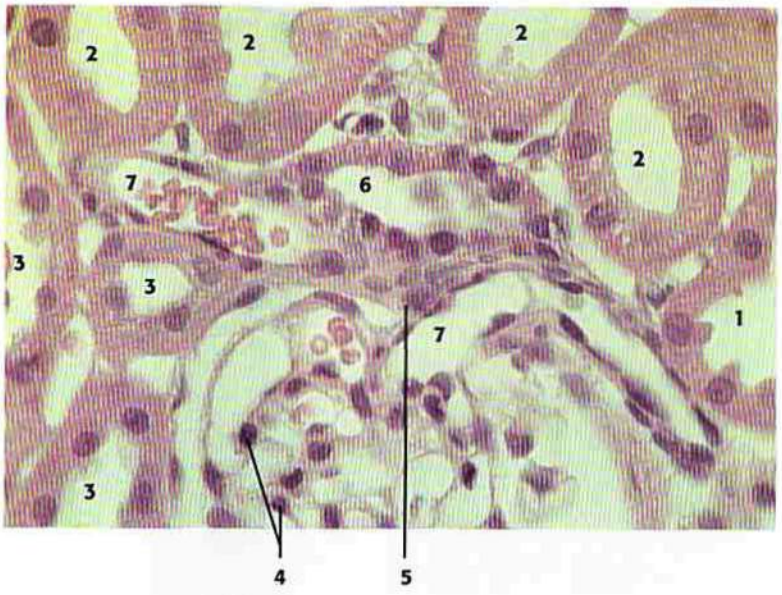


FIGURE 8-11. Juxtaglomerular apparatus. 1 = Macula densa; 2 = PCT; 3 = DCT; 4 = intraglomerular mesangial cells; 5 = extraglomerular mesangial cells; 6 = thick afferent limb; 7 = efferent arterioles. (Courtesy of Uniformed Services University of the Health Sciences.)

FLASH FORWARD

Angiotensin II → cells contract → vasoconstriction and reduced glomerular flow.
Natriuretic factor → cells relax → vasodilation and increased glomerular flow.

in the walls of the afferent and efferent arterioles (see Figure 8-11). The JGA functions to control GFR in response to BP in the afferent arterioles.

Macula Densa

A specialized group of epithelial cells in the distal tubules that come in close contact with the afferent and efferent arterioles. The cells of the macula densa are sensitive to sodium concentration and rate of flow through the DCT, and regulate GFR through locally active hormones. (See physiology section for detailed explanation of the renin-angiotensin-aldosterone system.)

KEY FACT

Despite large fluctuations in arterial BP (75–160 mmHg), the GFR only changes a few percentage points.

Juxtaglomerular Cells

Specialized myoepithelial cells located in the afferent arterioles. These cells act as baroreceptors (they sense intra-renal pressure), which enables them to efficiently monitor BP and maintain normal glomerular filtration rate (GFR) through the release of renin, the initial catalytic enzyme in the renin–angiotensin system.

Extraglomerular Mesangial Cells

Contractile cells with receptors for both angiotensin II and natriuretic factor, thus enabling them to regulate glomerular flow.

KEY FACT

Surgeons pay special attention to ureteral peristalsis in order to identify and therefore avoid injury to the ureters during open and laparoscopic operations!

CALYCES, RENAL PELVIS, AND URETERS

These structures are lined with **transitional epithelium**. The muscular layer of the calyces, renal pelvis, and ureters are composed of helically arranged smooth muscle, which becomes more longitudinal as the ureters reach the bladder. The ureters exhibit peristaltic contractions as they pass urine from the kidneys to the bladder.

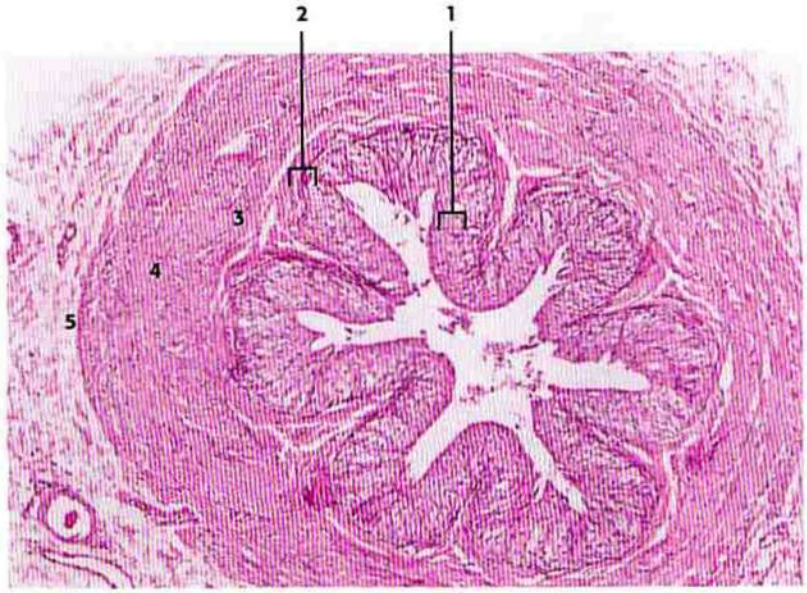


FIGURE 8-12. Histology of the bladder. 1 = Transitional epithelium; 2 = submucosa; 3 = inner longitudinal smooth muscle; 4 = middle circular smooth muscle; 5 = outermost longitudinal smooth muscle. (Courtesy of Uniformed Services University of the Health Sciences.)

BLADDER

The wall of the urinary bladder is composed of the following layers (see Figure 8-12):

- **Transitional epithelium:** Lines the inner surface of the bladder. Its thickness depends largely on the bladder's fullness (an empty bladder has much thicker transitional epithelium than its full, distended counterpart).
- **Smooth muscle:** There are three layers of smooth muscle arranged in all dimensions that comprise the wall of the bladder, which become three distinct layers of smooth muscle at the bladder neck. The innermost of these layers becomes the involuntary urethral sphincter at the junction between the bladder and the urethra.

CLINICAL CORRELATION

Micturition is controlled autonomically by the internal sphincter and voluntarily by the external sphincter. Problems with these muscles can lead to incontinence.

Physiology

CONCEPTS OF TRANSPORT AND WATER METABOLISM

Standardized Units of Measurement

- **Quantity** of a given substance in a solution (**solute**) is expressed through **millimoles (mmol), milliequivalents (mEq),** or **milliosmoles (mOsm).**
- **Concentration** of a given substance in a solution reflects quantity per given volume. Commonly used units include: **mmol/L, mEq/L,** and **mOsm/L.**

Definitions

- One **mole** represents 6×10^{23} **molecules of a neutral substance.**

  1 mmol = 1/1000 of a mole

- An **equivalent** describes the **quantity of ionized (charged) molecules** in a given solution.

For example, one mole of **NaCl** in a solution will dissociate into one equivalent of Na and one equivalent of Cl. However, one mole of $MgCl_2$ will dissociate into two equivalents of Mg and two equivalents of Cl.

1 mole NaCl = 1 Eq (Na) + 1 Eq (Cl)
Therefore: **1 mole (Na) = 1 Eq (Na)**
1 mole $MgCl_2$ = 2 Eq (Mg) + 2 Eq (Cl)
Therefore: **1 mole (Mg) = 2 Eq (Mg)**

KEY FACT

Osmolarity ≠ Molarity
10 mmol glucose = 10 mOsm/L glucose
10 mmol NaCl = 20 mOsm/L NaCl (NaCl is ionic and dissociates into Na^+ and Cl^-)

- An **osmole** defines the number of single particles into which solute will dissociate in solution. Accordingly, **osmolarity** will represent the concentration of those particles per given volume (e.g., **Osm/L**).

Keeping in mind the above example, the osmolarity of non-ionic substances will equal its molarity, while it will differ in the cases of ionic (charged substances).

Forms of Transport

Concepts of Transport

There are two main types of transport: transcellular and paracellular.

- **Transcellular transport**: Substances are transported across both the apical and basolateral membranes and through the cytoplasm of the cell.
- **Paracellular transport:** The transported substances travel through the tight junctions *between* cells. This form of transport involves **simple diffusion** and/or **carrier-mediated diffusion**.

Substances can be transported via passive or active transport.

Passive Transport

Relies solely on the concentration gradient across the cell membranes as the driving force (does not require energy).

- **Simple diffusion** is defined by the **rate of diffusion**, or how fast the molecules move across the membrane. The **net transfer** of solute is directed **down** the **concentration gradient**, and continues until the state of equilibrium is reached. At this point, the rate of transfer across the membrane becomes equal in both directions.
- **Facilitated diffusion** is a **carrier-mediated** process directed **down** the **concentration gradient**. The carriers are specific membrane proteins that exhibit a high affinity for the substance. However, the amount of carrier is limited, and therefore the **transport rate** does not increase continuously with the increasing concentration gradient. Rather, a maximum rate of transport, defined as **the transport maximum** (T_m) for a given substance, is achieved when all carrier sites are saturated.

In facilitated diffusion, molecules with structural similarities may **compete** for the transport carrier binding site, thus reducing the transport rate of the preferred solute. This provides the basis for **competitive agonist/antagonist actions**.

KEY FACT

Examples of substances of physiologic importance that cross the membrane by non-ionic diffusion include **CO_2** and **NH_3**. These compounds play important roles in renal regulation of acid–base balance.

- **Non-ionic diffusion** is a passive process by which impermeant ions derived from the dissociation of weak acids or bases can cross cell membranes. (The equation: $HA = [H^+] + [A^-]$ depicts the state of equilibrium between the undissociated and dissociated forms of a weak acid.) Cell membranes are impermeable to ions, but permeable to the neutral undissociated free acid form. The system's equilibrium is based on the pH value across the membrane.

- **Osmosis** refers to diffusion of a solvent down its concentration gradient.
  - **Osmotic pressure** is the hydrostatic pressure which must be physically applied to the side of a semipermeable membrane containing high-solute concentration (low-water concentration) in order to prevent the osmotic flow of water across the membrane.
  - Osmosis is the only mechanism by which **water** is transported across the renal tubular epithelium.

Active Transport

Substances transported against their electrochemical gradient require a specific carrier and energy source, the most important of which is ATP.

- **Primary active transport:** Requires a **specific ATPase** transporter. The **Na^+,K^+-ATPase** and the **Ca^{++}-ATPase** systems are found on the basolateral membrane of the renal tubules. This allows for Na^+ to be transported in one direction only (from the tubular lumen to the renal interstitial fluid).
- **Secondary active transport:** Two different substances **simultaneously bind to the same membrane carrier** and are concurrently transported across the membrane. The main differentiating factor between primary and secondary active transport is that in the latter, one of the substances moves down its electrochemical concentration gradient while the other moves up (opposite direction).
  - **Co-transport (symport)** in which two compounds use the same protein carrier and move in the same direction across the membrane (e.g., **Na^+-glucose**)
  - **Counter-transport (antiport)** transported substances are moved across the membrane in opposite directions (e.g., **Na^+-H^+** counter-transport in the proximal tubule, and the distal tubular **H^+-K^+** antiporter).

Rate-Limited Transport

The **concept of T_m** (as described previously) applies to both secretory and reabsorptive epithelial cell transport mechanisms. The different ways in which T_m applies to glucose and PAH are discussed later.

KEY FACT

Potassium is the main **cation** regulating **ICF**;
Proteins and **organic phosphates** are the main **anions** in **ICF.**
Sodium is the main cation regulating **ECF;**
Cl^- and HCO_3^- are the main **anions** in **ECF.**

Fluid Compartments

Composition of Extracellular Fluid (ECF) and Intracellular Fluid (ICF)

The ionic compositions of the ECF and ICF (see Figure 8-13) are remarkably different. However, the osmolarity of the compartments is virtually equal, which allows for normal cell homeostasis. These concentration gradients across cell membranes are maintained by transport mechanisms.

KEY FACT

TBW = ECF + ICF

The fluid component of the body is divided into several compartments (see Figure 8-14). Water accounts for 60% of a person's total weight (known as **total body water** or **TBW**). Two-thirds of TBW (40% of total body weight) is intracellular fluid (ICF) and one third (20% of total body weight) is extracellular fluid (ECF).

KEY FACT

60–40–20 rule: TBW = 60%, ICF = 40%, and ECF = 20% of body weight.

In a 70-kg adult, assuming normal hydration, 42 liters (60%) of their body weight is water, of which 28 liters (66.7%) is in the intracellular space and 14 liters (33.3%) is in the extracellular space.

- TBW varies based on age, sex, and body fat percentage. As body fat increases, the relative percentage of their TBW decreases.
- **Infants and children** have higher TBW than adults due to a decreased proportion of fat. At birth, the ECF compartment consists of almost 50% of the TBW.

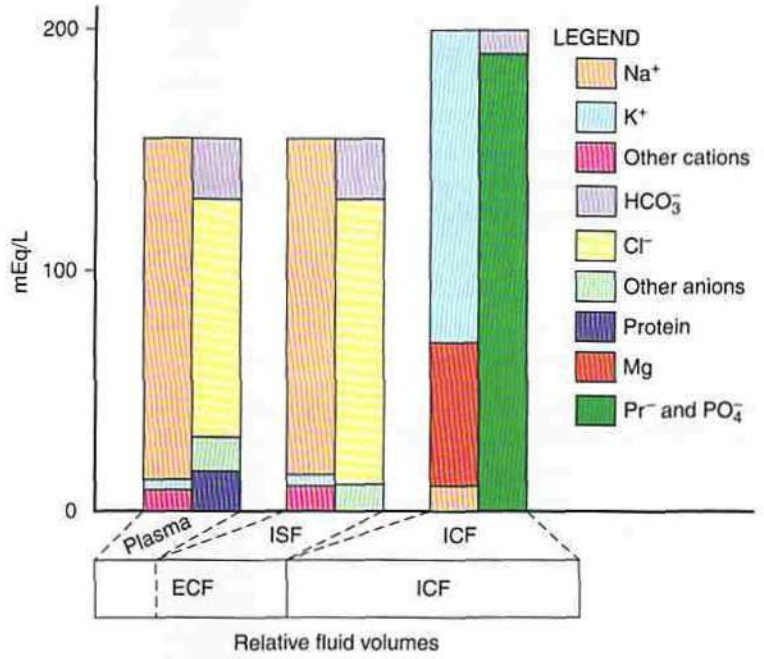


FIGURE 8-13. Composition of body fluids. ECF = Extracellular fluid; ICF = intracellular fluid; ISF = interstitial fluid. (Modified, with permission, from Hay WW et al. *Current Pediatric Diagnosis & Treatment*, 18th ed. New York: McGraw-Hill, 2007.)

- **Aging** is commonly associated with an increase in body weight in the form of fat (decreased TBW).
- **Females**, on average, have more body fat than males, and therefore have lower TBW.

The **ECF compartment** is further divided into interstitial fluid, transcellular fluid, and plasma (see Table 8-4).

- **Interstitial fluid** (75%): Water within the body but outside the cells.
- **Plasma** (25%): Non-cellular fluid of the blood.
- **Transcellular fluid:** CSF, synovial fluid, aqueous humor, and pericardial and peritoneal fluids.

KEY FACT

Estimating content of fluid compartments:
TBW (L) = 0.60 × wt (kg)
ICF = 0.40 × wt (kg)
ECF = 0.20 × wt (kg)

Estimating and Measuring Fluid Compartment Volume

Estimating Body Fluid Volumes

The percentage of the fluid compartment multiplied by the total weight (assuming normal hydration).

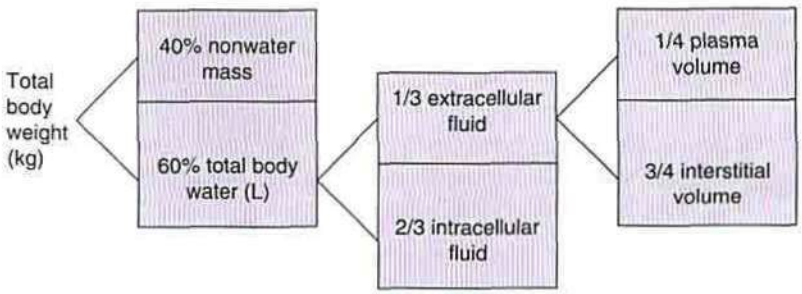


FIGURE 8-14. Fluid compartments.

TABLE 8-4. Comparison of the Composition of ICF and ECF

Fluid Compartment	Composition
ICF	▪ Potassium, magnesium, phosphate ions, organic anions, and protein ▪ Slight negative charge, due to the nature of the cell membrane
ECF	▪ Sodium, chloride, bicarbonate, and calcium ▪ Slight positive charge, due to the nature of the cell membrane

Measuring Body Fluid Volumes

Accomplished by injecting a known amount of a measurable molecule into the fluid space and allowing it to diffuse. The ideal molecule will enter the respective space and remain there (without diffusing into other spaces). Each compartment has its own unique molecule, which is used as an indicator for the respective compartments. Expected physiologic values are depicted in Table 8-5.

- **TBW indicators:** D_2O (heavy water), ^3H_2O tritium (radioactive water), and $C_{11}H_{12}N_2O$ (antipyrine).

$$TBW = ECF + ICF$$

The volume is calculated by applying the **indicator dilution principle** in which the distribution volume (V) for the indicator equals the quantity of indicator (i.e., ^3H_2O) divided by concentration (C) of indicator.

$$V = Q/C$$

- **Plasma volume (PV) indicators:** Evans-blue dye or radioiodinated human serum albumin (^{125}I-albumin).
- **Blood:** (Plasma volume) / (1 – hematocrit).
- **ECF Indicators:** Inulin, mannitol and ^{22}Na.

$$ECF = Plasma + Interstitial\ fluid.$$

KEY FACT

Osmolarity of ECF and ICF.
ECF osmolarity = ICF osmolarity.
ICF volume changes to maintain this balance.

TABLE 8-5. *Normal Values of Fluid Compartments Based on a 70-kg Patient* with a Plasma Osmolarity of 280 mOsm/L

Compartments	Volume (L)	Concentration (mOsm/L)	Total (mOsm)
TBW	42	280 (300)	11,760
ECF	14	280 (300)	3920
ICF	28	280 (300)	7840

Intercompartmental Water Dynamics (see Figure 8-15).

In a steady state, the osmolarity of ECF is equal to that of ICF.

- Under normal physiologic conditions, substances such as mannitol, NaCl, and $NaHCO_3$ are confined to the ECF and they do not readily cross the cell membrane.
- Under certain pathophysiologic conditions, this steady state is interrupted.

KEY FACT

Osmolarity = Concentration of osmotically active particles per unit volume.

Normal value for body fluid osmolarity (BFO) is 290 mOsm/L (for practical purposes = 300 mOsm/L).

Volume changes take place in the ECF only. These compartmental disturbances can be divided into two major groups:

- **Volume contraction** refers to loss of water from the ECF.
- **Volume expansion** refers to increase in the ECF volume due to water "leaking in."

Furthermore, this can be subdivided based on the osmolarity of ECF into **iso-osmotic, hypo-osmotic,** and **hyperosmotic** disturbance (all depicted in Figure 8-16, the Darrow–Yannet diagram), followed by practical calculations (see Table 8-6).

ECF Pathophysiology Key Facts

- **Iso-osmotic volume contraction:** Prolonged watery diarrhea → hypovolemia and low flow state → activation of the renin-angiotensin-aldosterone system (RAAS) → lowered urinary output (to retain Na^+ and H_2O).
- **Hypo-osmotic volume expansion:** Distinguish between **psychogenic polydipsia/water intoxication** and **diabetes insipidus (DI)** with water restriction.
  - If psychogenic polydipsia is present, an appropriate response in water and Na^+ retention is expected.

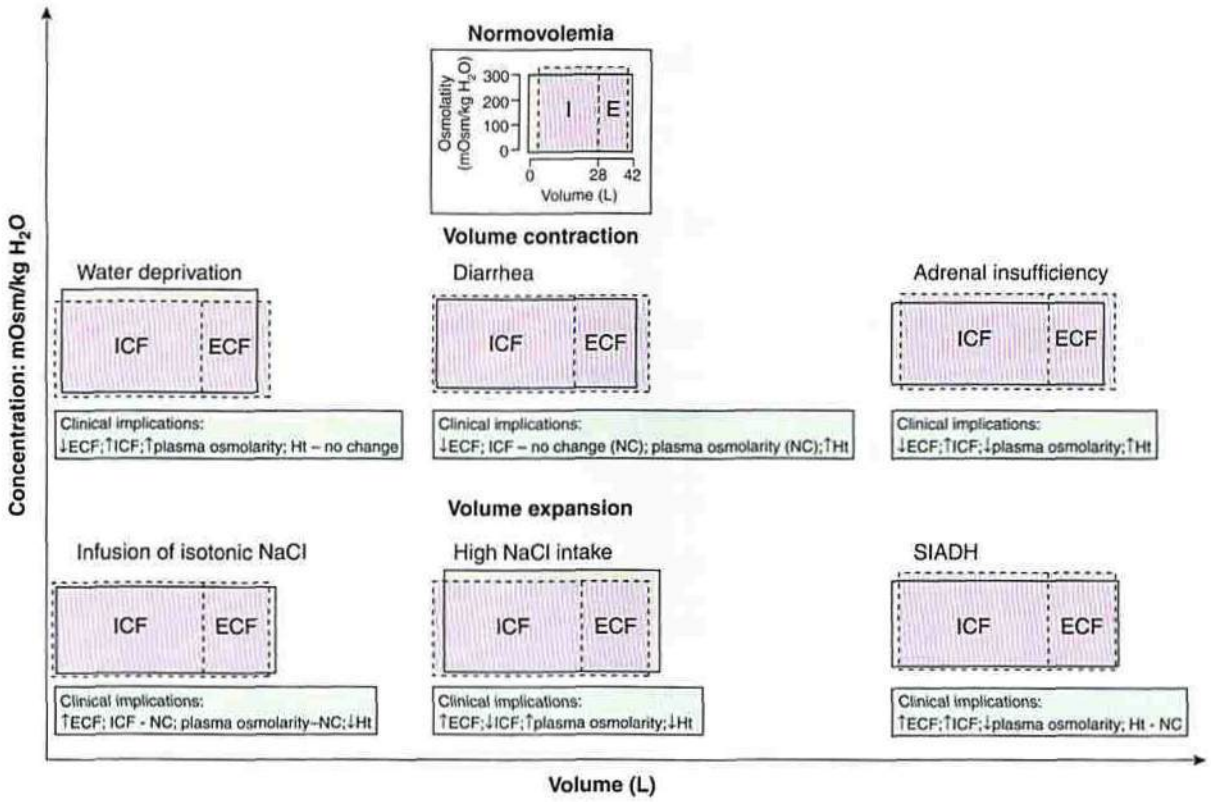


FIGURE 8-15. Darrow-Yannet diagram and pathophysiology of intercompartmental water dynamics.

TABLE 8-6. Sample Calculations

Normal physiologic conditions, normal hydration:

TBW = 0.6 × (70 kg) = 42 L

ICF volume = 0.4 × (70 kg) = 28 L

ECF volume = 0.2 × (70 kg) = 14 L

Body fluid osmolarity (BFO) = 300 mOsm/kg

Total body osmoles = (TBW) × (BFO) = (42 L) (300 mOsm/kg H_2O) = 12,600 mOsm

ICF osmoles = (ICF) × (BFO) = (28 L) (300 mOsm/kg H_2O) = 8400 mOsm

ECF osmoles = (ECF) × (BFO) = (14 L) (300 mOsm/kg H_2O) = 4200 mOsm

Example for SIADH = water intoxication = Hypo-osmotic volume expansion:

Assume an extra 6 L of H_2O reabsorption:

Redistribution of H_2O, secondary to volume overload with H_2O.

TBW (L) = 0.6 × (70 kg) = 42 L + 6 = 48 L

ICF (L) = 0.4 × (70 kg) = 28 L + 4 L ($^2/_3$ of 6 L) = 32 L

ECF (L) = 0.2 × (70 kg) = 14 L + 2 L ($^1/_3$ of 6 L) = 16 L

Compare:

Normal osmolarity: 12,600 mOsm/42 L TBW = 300 mOsm/kg

SIADH osmolarity: 12,600 mOsm/48 L TBW = 262.5 mOsm/kg

SIADH ICF volume: (ICF osm)/(SIDH osmolarity) = 8400 mOsm/262.5 mOsm/kg = 32 L

SIADH ECF volume: (ECF osm)/(SIDH osmolarity) = 4200 mOsm/262.5 mOsm/kg = 16 L

Final picture:

Increase in both ECF and ICF volumes.

Decrease in body osmolarity (plasma protein dilution).

Hematocrit does not change: Concentration of RBCs decreases; however, RBC volume increases, so H_2O shifts into the cells.

- **Heat-acclimated** individuals generally produce hypotonic sweat, thus do not waste Na^+, allowing electrolyte levels to remain within normal limits. Those who are not heat-acclimated may have a higher concentration of NaCl in their sweat and may become **hyponatremic** and/or **hypochloremic**, in addition to **volume depleted** (dehydrated).

In both cases, however, there is an appropriate activation both of RAAS and antidiuretic hormone (ADH).

GENERAL RENAL PHYSIOLOGY

Renal Clearance: General Concepts

Renal Clearance (C_x)

Volume of plasma cleared of a given substance by the kidney per unit time:

$$C_x = U_x V / P_x$$

where C_x is the clearance rate of substance X (mL/min), U_x is the urine concentration of substance X (mg/mL), V is the urine flow rate (mL/min), and P_x is the plasma concentration of substance X (mg/mL).

It can be determined how a specific substance is handled by the renal tubules by comparing the clearance rate of a substance with the GFR (see Table 8-7).

TABLE 8-7. Interpreting Cx

C_x > GFR	Substance filtered and with net secretion.
C_x < GFR	Substance filtered and partially reabsorbed.
C_x = GFR	Neither is dominant: the substance does not appear in the urine.

Inulin, a fructose polymer, possesses some unique properties (described later), and can be used to determine the clearance of any substance by comparing it to the inulin clearance, expressed through the **clearance ratio**.

$$\text{Clearance ratio} = C_x/C_{inulin}$$

C_x/C_{inulin} = 1.0 indicates that the clearance of substance X is equal to that of inulin; the substance is neither secreted nor reabsorbed. Substances with these properties are called **glomerular markers**.

C_x/C_{inulin} < 1.0 indicates that the clearance rate of substance X is lower than that of inulin, suggesting two possibilities:

- The substance is **not filtered** (e.g., albumin).
- The substance **is filtered**, but is subsequently **reabsorbed** (e.g., glucose, amino acids, urea, phosphate, Na^+, Cl^-, and HCO_3^-).

C_x/C_{inulin} > 1.0 indicates that the substance **is filtered and excreted** (e.g., organic acids, bases, and in some cases K^+).

Glomerular Filtration Barrier

Glomerular filtration is closely regulated by the barrier (see Figure 8-16) that separates the blood from Bowman's space and is composed of three main layers:

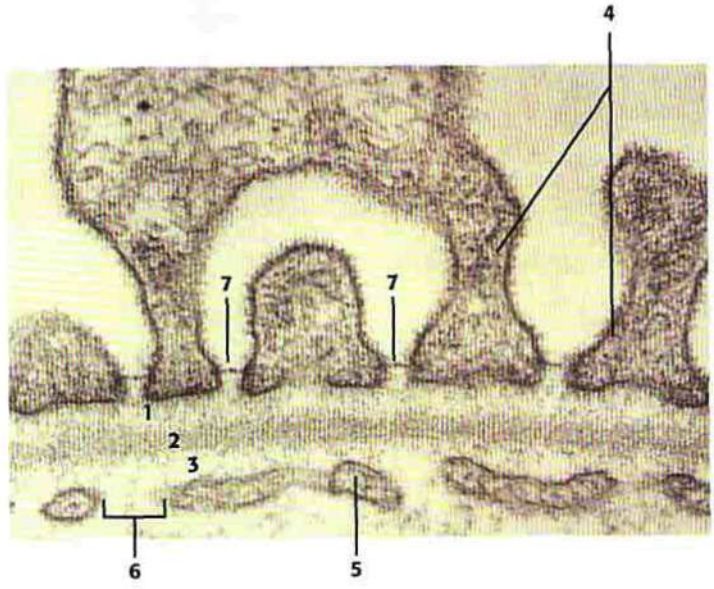


FIGURE 8-16. Electron photomicrograph of the glomerular filtration barrier. 1 = Lamina rara externae; 2 = lamina densa; 3 = lamina rara interna; 4 = pedicels; 5 = capillary endothelium; 6 = endothelial pore; 7 = filtration slit membrane. (Courtesy of Dr. Ruth Bulger, Uniformed Services University of the Health Sciences.)

- **Capillary endothelium** originates from the afferent arteriole and exits via the efferent arteriole. This is a non-diaphragm fenestrated endothelium that lines the inside of the capillary.
- **Glomerular basement membrane (GBM)** is composed of types IV and V collagen, laminin (glycoprotein), and heparan sulfate (proteoglycan). Laminin and heparan sulfate account for the GBM's **negative charge**, thus keeping plasma proteins, which have a slight negative charge, from entering Bowman's space. The basement membrane is composed of **three layers**: lamina rara interna, lamina densa, and lamina rara externa.

CLINICAL CORRELATION

The charge barrier is **lost** in **nephrotic syndrome,** thus allowing proteins to leak out of the capillaries, and leading to **albuminuria, hypoproteinemia, generalized edema,** and **hyperlipidemia.**

Glomerular Filtrate

Material filtered through the glomerular filtration barrier, created at a rate of **125 mL/min**. The glomerular filtration barrier is relatively impermeable to proteins, thus the filtrate solution contains little protein. Certain molecules, such as calcium and fatty acids, which are bound to plasma proteins, will have a lower-than-expected concentration within the filtrate. Several other factors determine whether a substance will pass through the filtration barrier:

- Molecular size
- Shape
- Charge
- Hemodynamic conditions

FLASH FORWARD

The α-3 chain of collagen type IV, the target antigen in Goodpasture's syndrome, is a common component of the GBM and the alveolar basement membrane.

Glomerular Filtration Rate

Represents renal clearance of a substance that is **neither reabsorbed nor secreted** by the nephron.

- **Inulin** is the gold standard when measuring GFR because it is freely filtered, and neither reabsorbed nor secreted (**glomerular marker**).
- **Creatinine** (end product of muscle metabolism) is a more clinically useful alternative for **estimating** GFR. While a small amount of creatinine is secreted by the renal tubules, resulting in an overestimation of the urine creatinine concentration, the plasma creatinine measurement often overestimates the actual amount of creatinine in the blood. These two overestimations cancel each other out, thus providing reliable estimation of GFR.
- **Blood urea nitrogen (BUN)** is often used to estimate GFR.

$$GFR = U_{inulin}V/P_{inulin} = C_{inulin}$$

$$GFR \approx U_{creatinine}V/P_{creatinine}$$

where U is the concentration in urine (mg/mL), V is the urine flow rate (mL/min), P is the concentration in plasma (mg/mL), GFR is the glomerular filtration rate (normal = 120 mL/min), and C_{inulin} is the clearance of inulin.

KEY FACT

Creatinine clearance is an estimation of GFR.

CLINICAL CORRELATION

Decreased GFR (e.g., acute renal failure; ARF) leads to an elevation of both BUN and creatinine concentrations in the blood.

Renal Blood Flow

The blood flow to the kidneys represents approximately 25% of the total cardiac output. Based on an average cardiac output of 5 L/min, the kidneys will receive 1.25 L/min, or 1800 L/day. Because the kidneys handle the blood volume many times over each day, they play a crucial role in systemic blood circulation, as well as maintaining normal body fluid volume and composition.

The kidney contains numerous **nephrons with vasculature connected in series** (see Figure 8-17). Blood flow to the nephrons is supplied by afferent arterioles branching off interlobular arteries within the kidney. Plasma is fil-

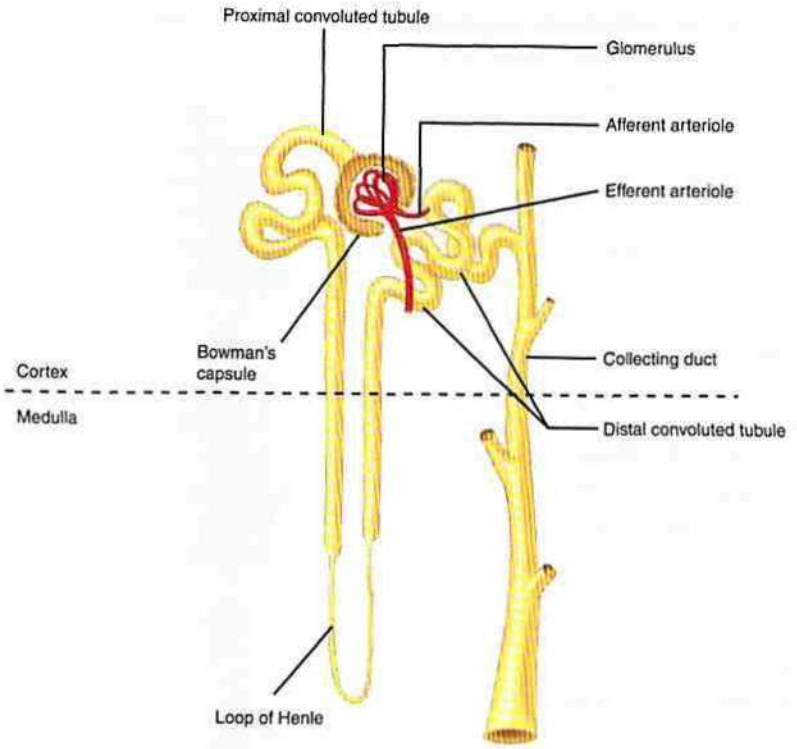


FIGURE 8-17. Nephron structure.

tered in the glomerular capillary bed, and the filtered blood flows out into the interlobular veins via the efferent arterioles.

- The average **afferent arteriole pressure is 85 mmHg.**
- The average **efferent arteriole pressure is 60 mmHg.**

Regulation Mechanisms

Systemic BP and perfusion dramatically impact renal function. Physiologic changes in Starling forces, renal vascular resistance, and hydrostatic pressures allow for **regulation** of renal blood flow (RBF) and function (see Table 8-8).

Influencing Factors

The sympathetic nervous system, hormones, and various drugs influence renal function.

- **Sympathetic nervous system:** Exerts its action via the catecholamines **epinephrine and norepinephrine,** which activate α_1 **receptors,** thus causing vasoconstriction of the renal arterioles (efferent > afferent), and a decrease in RBF and GFR. Moderate sympathetic stimulation will not result in change in GFR.
- **Prostaglandins/bradykinin:** PGE_2 and PGI_2 (both produced in the kidneys) cause dilatation of both the afferent and efferent arterioles, thus increasing RBF and GFR. **NSAIDs inhibit prostaglandin** synthesis and interfere with these protective effects of prostaglandins (GFR is reduced).
- **Angiotensin II:** A potent vasoconstrictor that preferentially vasoconstricts the efferent arteriole. The mechanism is dose-dependent; angiotensin II can cause either an **increase in GFR** (only efferent arterioles affected) or a **decrease in GFR** (both afferent and efferent arterioles are affected).
- **Dopamine** (precursor of norepinephrine) dilates the vessels and suppresses sodium reabsorption in the proximal tubule by inhibiting the action of the

TABLE 8-8. Renal Function and Blood Flow

Effect	GFR	Renal Plasma Flow (RPF)	Filtration Fraction (GFR/RPF)
Afferent arteriole constriction	⇓ due to ⇓ P_{GC}	⇓	No change
Afferent arteriole dilation	⇑ due to ⇑ P_{GC}	⇑	No change
Efferent arteriole constriction	⇑ due to ⇑ P_{GC}	⇓	⇑
Increased plasma protein concentration	⇓ due to ⇑ π_{GC}	No change	⇓
Decreased plasma protein concentration	⇑ due to ⇓ π_{GC}	No change	⇑
Constriction of ureter or urinary tract obstruction	⇓ due to ⇑ P_{BS}	No change	⇓

P_{GC} = glomerular capillary hydrostatic pressure; P_{BS} = Bowman's space hydrostatic pressure; π_{GC} = glomerular capillary plasma colloid osmotic pressure; π_{BS} = Bowman's space interstitial colloid osmotic pressure.

basolateral Na^+-K^+-ATPase pump. Dopamine is released directly by the proximal tubule in response to a rise in BP, resulting in increased RBF and GFR.

Autoregulation Mechanisms

Autoregulation is the process by which an organ maintains relatively constant blood flow despite variations in BP. These mechanisms typically have limits outside of which they are ineffective.

The kidney has two proposed autoregulatory mechanisms: **Stretch (myogenic)** and **tubuloglomerular feedback**.

- **Stretch mechanism:** When BP increases, arterioles in the kidney are stretched. This leads to vasoconstriction of the afferent arteriole, which maintains constant RBF.
- **Tubuloglomerular feedback mechanism:** Increased arterial pressure leads to increased RBF, and increased flow to the distal tubule, which is sensed by the macula densa. Through a variety of mechanisms, the macula densa causes vasoconstriction of the afferent arteriole, thus attenuating RBF and closing the negative feedback loop.

Measurement of Renal Plasma and Blood Flow

Renal Plasma Flow

A measure of the volume of plasma that flows through a single nephron in a given amount of time. If a substance could be cleared completely from the plasma, its clearance rate could be used to calculate the true renal plasma

flow (RPF). However, RPF cannot be directly determined because there is no known substance that is cleared completely from the kidney.

- **Para-aminohippuric acid (PAH)** is an endogenous substance that is 90% excreted from plasma through the kidneys through both filtration and secretion. The amount of PAH in plasma in the renal artery is equal to the amount of PAH in urine. Therefore, the clearance rate of PAH can be used to calculate the effective renal plasma flow **(ERPF).**

$$\text{ERPF} = (U_{PAH} \times V) / P_{PAH} = C_{PAH}$$

where U_{PAH} **is the Urine concentration of PAHV is the Urine flow rate** P_{PAH} **is the Plasma concentration of PAH** C_{PAH} **is the Clearance rate of PAH.**

ERPF can be used to calculate the value of true RPF and RBF.

True Renal Plasma Flow

The ERPF is an approximation of the true renal plasma flow. Because only 90% of PAH is cleared, the true value of renal plasma flow is underestimated by 10%. Therefore true RPF can be calculated as:

$$\text{True RPF} = \text{ERPF}/0.9$$

Renal Blood Flow

Renal plasma flow can be used to determine RBF, which represents the volume of blood flowing through a single nephron in a given period of time. RBF can be determined using the equation:

$$\text{RBF} = (\text{RPF})/(1 - \text{hematocrit})$$

- **Filtration fraction (FF)** is the fraction of plasma filtered across the membrane of the glomerular capillaries. It can be calculated if the GFR and the RPF are known:

$$\text{FF} = \text{GFR}/\text{RPF}$$

where GFR is the Glomerular filtration rate and RPF is the Renal plasma flow.

Normally, the calculated value of the FF is approximately 0.20. Therefore, about 20% of the RPF enters the glomerular capillaries, while the remaining 80% leaves the glomerulus via the efferent arteriole.

Changes in Filtration Fraction

Changes in the FF alter the plasma protein concentration, and thereby the osmolarity within the peritubular capillaries (see Figure 8-18). An increase in FF reduces the amount of plasma flowing into the peritubular capillaries. FF can be adjusted by changes in either RPF or GFR.

- **Renal vascular resistance** and the **hydrostatic pressure** differential between the renal artery and vein affect the flow of blood throughout the nephrons. Each parameter is inversely proportional to the other:
  - **Increased vascular resistance → decreases RPF.**
  - **Decreased vascular resistance → increased RPF** (provided the hydrostatic pressure differential is held constant).

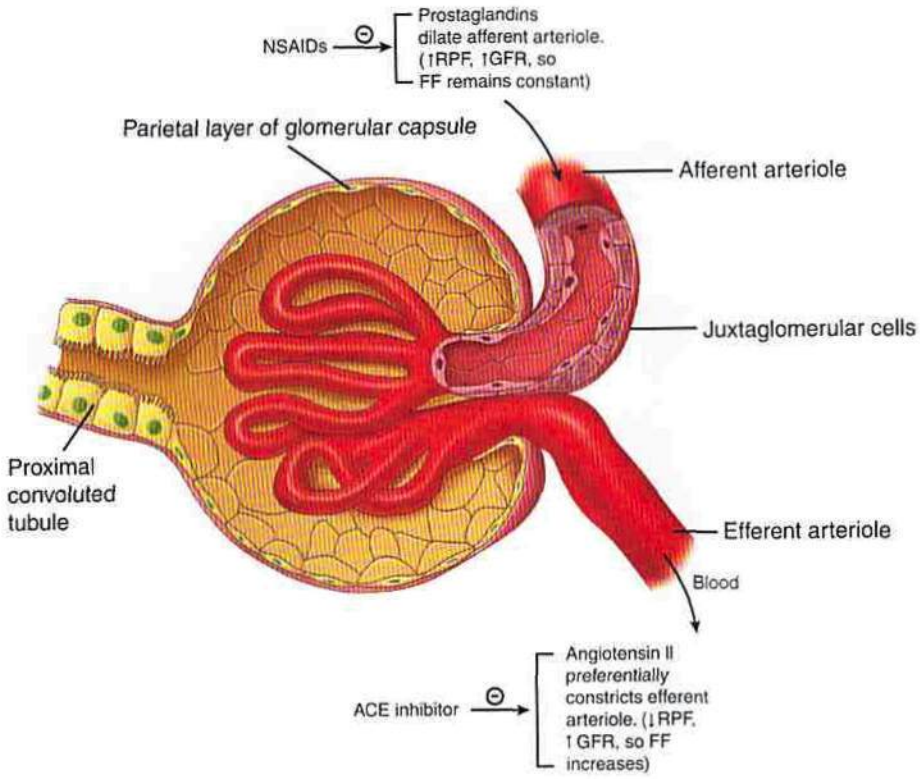


FIGURE 8-18. Effects of medications and hormones on renal plasma flow.

Changes in renal arterial and venous pressures can affect the FF; however, the autoregulatory mechanisms of the kidney efficiently maintain the pressures within relatively constant and narrow range.

Additionally, the rate of filtration across the glomerular capillaries is dictated by the net differential in **Starling forces (which oppose filtration)**, and is maintained by plasma protein concentration (**oncotic pressure**; see Figure 8-19).

GFR can be calculated by applying the **Starling equation**:

$$GFR = K_f[(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$$

where K_f is the Filtration coefficientP_{GC} is the Glomerular capillary hydrostatic pressureP_{BS} is the Bowman's space hydrostatic pressureπ_{GC} is the Glom-

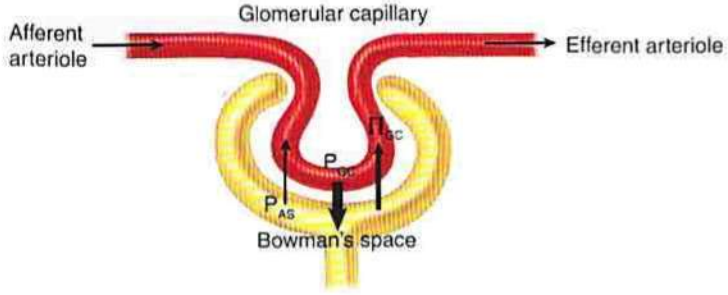


FIGURE 8-19. *Example of Starling forces acting on glomerular capillaries of a single nephron provided net pressure ≈ 0 mmHg and filtration equilibrium.* Average values: P_{GC} = 45 mmHg; P_{BS} = 10 mmHg; π_{GC} = 27 mmHg.

KEY FACT

The FF and Starling forces acting within the peritubular capillary act as the main "messengers" between the glomerulus and the proximal tubule.

KEY FACT

Glucosuria is an important clinical clue in the diagnosis of **diabetes mellitus (DM).**

erular capillary plasma colloid osmotic pressure π_{BS} is the Bowman's space interstitial colloid osmotic pressure (usually π_{BS} is zero because most protein is not filtered).

Concepts of Reabsorption and Secretion

Glucose

Completely reabsorbed in the **proximal tubules**. However, when serum glucose levels reach about 200 mg/dL, the reabsorption mechanism becomes overwhelmed and glucose may be excreted in the urine (this phenomenon is known as **splay**, or the excretion of a substance in small amounts before the **transport maximum** [T_m] is reached). At serum glucose levels exceeding 350 mg/dL, the transport mechanism becomes completely saturated, resulting in clinical **glucosuria** (see Figure 8-20).

Amino Acids

Reabsorbed by secondary active transport in the **proximal tubules**. The transport mechamism is T_m-limited), and saturation may result in the excretion of amino acids in the urine.

In general, amino acids are not found in the urine unless the individual has a genetic transport deficiency.

Urea

A waste product from the metabolism of amino acids, excreted in large amounts in the urine, and minimally reabsorbed. Urea contributes to the formation of **hyperosmolar urine** through its unique recirculation pathway, thus contributing to the maintenance of proper corticopapillary osmotic gradient (see Figure 8-27, depicting the countercurrent multiplier system, CCMS).

Para-Aminohippuric Acid

A substance that is both freely filtered through the glomerulus, and secreted from the peritubular capillaries into the tubular lumen. PAH is not reabsorbed (see Figure 8-21). As a result, PAH is theoretically completely cleared from

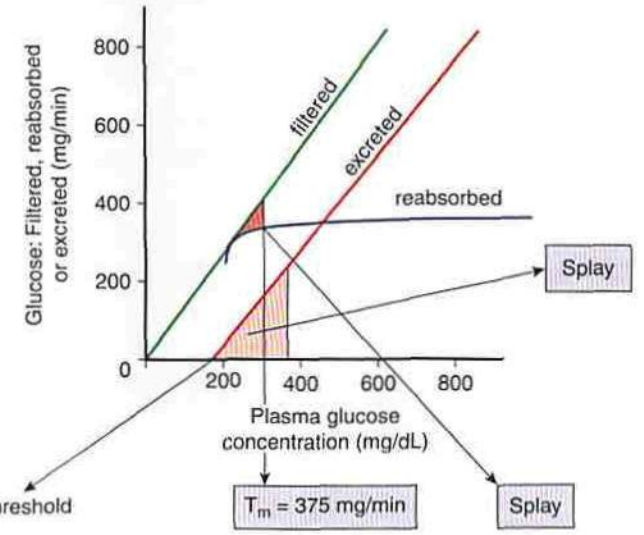


FIGURE 8-20. Glucose titration curve.

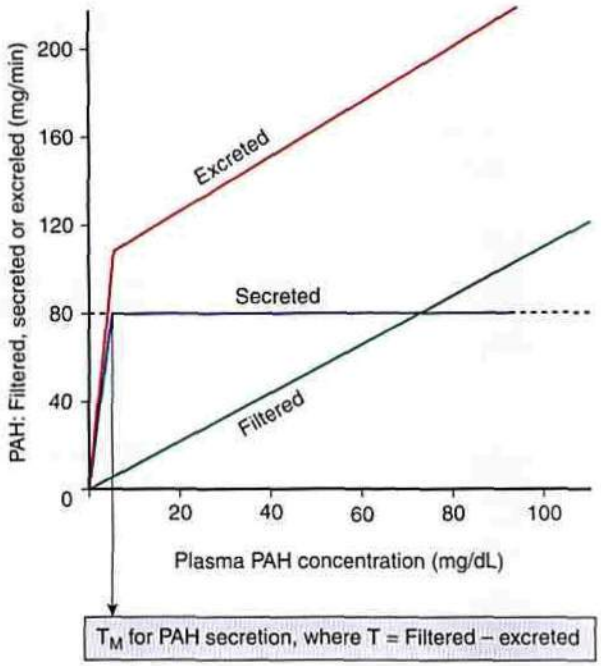


FIGURE 8-21. Para-aminohippuric acid titration curve.

the plasma and is used to estimate renal plasma flow (see earlier discussion of measurement of renal plasma and blood flow).

Free Water

Also referred to as solute-free water, it is produced in the thick ascending limb and the early distal tubule of the kidney. In these diluting segments of the nephron, NaCl is reabsorbed and the free water remains in the tubules to be excreted in the urine. As urine is produced, water and solutes are excreted in a somewhat independent manner. Excreted water can be determined by the urine flow rate (V) and the excreted solutes can be calculated using the osmolar clearance (C_{osm}):

$$C_{osm} = V - \frac{(U_{osm} \times V)}{P_{osm}}$$

where U_{osm} **is the Urine osmolarity and** P_{osm} **is the Plasma osmolarity.**

Free water clearance is equal to the difference between excreted water and osmolar clearance:

$$C_{H_2O} = V - C_{osm}$$

Urine Osmolarity

The clearance of free water can be used to estimate the kidneys' ability to concentrate or dilute urine.

- When C_{H_2O} **is positive**, excess water is excreted and urine is dilute.
- When C_{H_2O} **is negative**, excess solutes are excreted, water is retained, and urine is concentrated.

In order to concentrate urine, high levels of ADH (vasopressin) are needed to increase the permeability of the distal tubule and the collecting ducts to water.

- In the **presence of ADH**, urine is **concentrated** (body conserving water).
- In the **absence of ADH**, urine is **dilute.**

Nephron Physiology and the Tubular System

The **nephron unit** is composed of the **glomerulus**, through which fluid is filtered from the blood, and the **tubular system**, where the filtered fluid is modified through reabsorption and secretion of various solutes to produce urine.

Glomerulus

A network of glomerular capillaries encased in the **Bowman's capsule.** Blood flows from the **afferent arteriole** into the glomerular capillaries, where it is either filtered into Bowman's space or continues to flow through the **efferent arteriole** and the peritubular capillary system.

The fluid that is filtered into Bowman's space flows into the tubular portion of the nephron. The tubule can be divided into several segments with different characteristics and functions. Each segment relies on the **basolateral Na^+-K^+-ATPase pump** to maintain low intracellular Na^+ concentration, establishing a Na^+ gradient for Na^+ movement into the cells.

Proximal Tubule

The major site of reabsorption (see Figure 8-22). The cellular mechanism of reabsorption is based on the **transmembrane Na^+ gradient**, thus providing energy for numerous **secondary active transport** mechanisms. Solutes and water are reabsorbed proportionally; therefore **tubular fluid leaving** the proximal tubule is **isosmotic.**

- Reabsorbs **all filtered glucose** and **amino acids**, 60%–70% of the filtered electrolytes and water, and 50% of filtered urea from the tubular fluid.

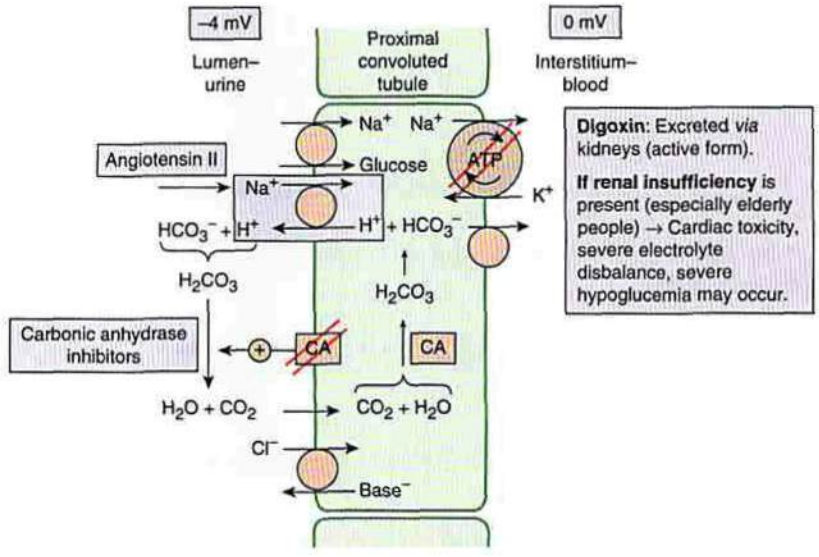


FIGURE 8-22. Early proximal convoluted tubule, "workhorse of the nephron." Reabsorbs all of the glucose and amino acids and most of the bicarbonate, sodium, and water. Secretes ammonia, which acts as a buffer for secreted H^+.

- Na^+ is reabsorbed via **cotransport** with amino acids, glucose, lactate, and phosphate, and via **countertransport** with HCO_3^- through the Na^+-H^+ exchanger.
- Ammonia is secreted to buffer the secreted H^+.
- Na^+ is reabsorbed with Cl^- in the **late proximal tubule**, driven by the lumen positive potential difference.
- Angiotensin II acts on the proximal tubule to stimulate Na^+ reabsorption, while atrial natriuretic factor blocks Na^+ reabsorption.

Loop of Henle

Consists of three portions: (1) thin descending; (2) thin ascending; and (3) thick ascending limbs. The majority of action occurs in the thick ascending limb of the loop.

- **Thin descending limb** reabsorbs about 20% of the filtered water, but no solute reabsorption occurs in this segment.
- **Thin ascending limb** is **impermeable** to **water** and has no significant reabsorption.
- **Thick ascending limb** is the **diluting segment** of the tubular system (see Figure 8-23). It is impermeable to water, yet reabsorbs solutes. This segment actively reabsorbs Na^+, K^+, and Cl^- via the **Na^+-K^+-2Cl^- cotransporter.** Reabsorbed K^+ leaks back into the lumen, creating a slight positive charge in the lumen fluid. This positive charge indirectly induces paracellular diffusion of Mg^{2+} and Ca^{2+} into the interstitial fluid.

Early Distal Convoluted Tubule

Cortical **diluting segment** of the tubular system (see Figure 8-24).

- The distal tubule transport mechanism relies on the Na^+–Cl^- cotransporter (situated on the luminal membrane), which provides the basis for Na^+, Cl^-, K^+, Ca^{2+}, and Mg^{2+} trafficking into and out of the lumen. This segment is impermeable to water and urea.
- The first part of this segment forms the **macula densa** of the juxtaglomerular complex, which provides **tubuloglomerular feedback** for autoregulation of RBF.
- **Angiotensin II** acts on the early distal tubule to stimulate Na^+ reabsorption, while **atrial natriuretic factor** blocks Na^+ reabsorption.
- **PTH** acts to increase active Ca^{2+} reabsorption.

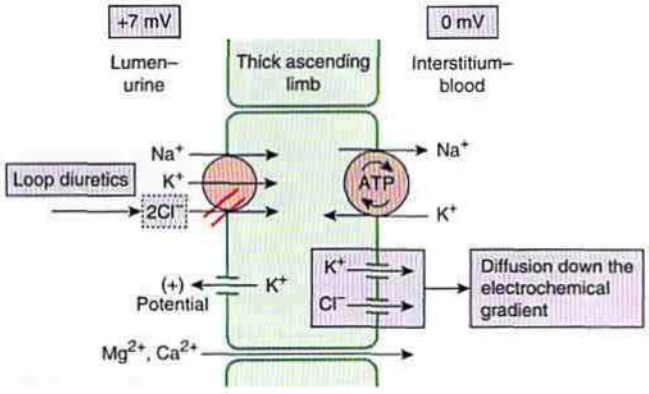


FIGURE 8-23. Thick ascending limb of Henle. This structure actively reabsorbs Na^+, K^+, and Cl^-, and indirectly induces the reabsorption of Mg^{2+} and Ca^{2+}. It is impermeable to water.

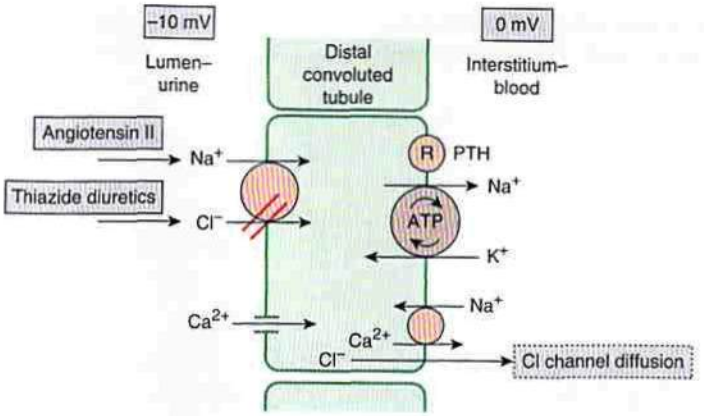


FIGURE 8-24. Early distal convoluted tubule. This structure actively reabsorbs Na^+ and Cl^-. Reabsorption of Ca^{2+} is under the control of parathyroid hormone.

Late Distal Tubule and Collecting Ducts

Composed of two cell types, principle and intercalated cells (see Figure 8-25).

KEY FACT

For each H^+ ion secreted into the lumen, one bicarbonate ion can be reabsorbed across the basement membrane into the interstitial fluid.

- **Principle cells** reabsorb Na^+ and water and secrete K^+ via the Na^+–K^+–ATPase pump.
- **Intercalated cells** are key players in **acid–base regulation** of body fluids, as they secrete H^+ and reabsorb K^+ and HCO_3^-. Carbonic acid can be formed in these cells via the catalytic action of carbonic anhydrase on H_2O and CO_2. The **carbonic acid** then dissociates into H^+ and bicarbonate. H^+ is secreted into the tubular lumen via the H^+–ATPase transport mechanism.

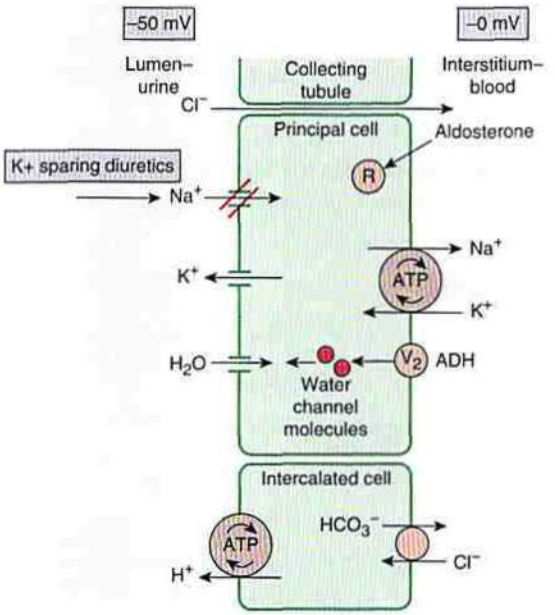


FIGURE 8-25. Collecting tubules reabsorb Na+ in exchange for secreting K+ or H+ (regulated by aldosterone). Reabsorption of water is regulated by ADH (vasopressin). Osmolarity of the medulla can reach 1200 mOsm.

- **Aldosterone** stimulates Na^+ reabsorption and K^+ secretion in the principle cells, as well as H^+ secretion in the intercalated cells.
- In the **presence of ADH (vasopressin)**, water channels are recruited and inserted into the luminal membrane of the principle cells, making them **permeable to water**. In the **absence of ADH**, the late distal tubule and the collecting ducts are **impermeable to water**. The presence or absence of ADH therefore controls the concentration or dilution of urine.
- **Urea** reabsorption only occurs in the inner medullary collecting ducts (the late distal tubules, the cortical collecting ducts, and the outer medullary collecting ducts are impermeable to urea). ADH increases urea permeability in the inner medullary collecting ducts.

KEY FACT

In humans, the maximum osmolarity at the tip of the loop reaches about 1200–1400 mOsm/L, half of which is attributed to NaCl and the rest to urea.

Countercurrent Multiplier System

The countercurrent multiplier system (CCMS) is a U-shaped structure that is an integral part of the nephron known as the **loop of Henle**. There are three loop regions within the CCMS (**thin descending limb, thin ascending limb,** and the **thick ascending limb**) responsible for establishing hyperosmotic renal medullary interstitial fluid through a multi-step process (see Figure 8-26):

KEY FACT

The role of the loop of Henle's multiplier system is to establish the hyperosmolarity of the renal medulla.

The term **countercurrent** describes the fluid movement in opposite directions in the two limbs of the loop, which magnifies the effect of transport from one limb on transport from the other limb.

Countercurrent Exchanger (Vasa Recta)

U-shaped capillaries are freely permeable to water and all solutes except protein. As a result, the vasa recta equilibrate readily with the surrounding inter-

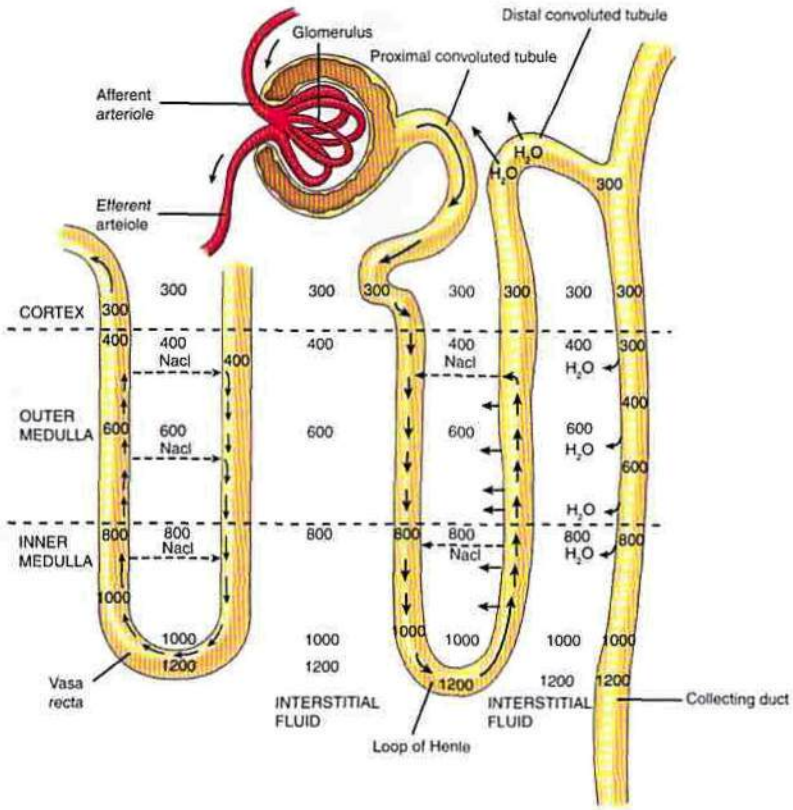


FIGURE 8-26. Countercurrent multiplier system and vasa recta, the countercurrent exchanger.

KEY FACT

The role of the vasa recta is to preserve the hyperosmolarity of the renal medulla.

stitial fluid. They enter the renal medulla, at the point of high interstitium solute concentration, and are situated in close proximity to the loop of Henle. This enables the formation of the **cortico-medullary osmolar concentration gradient** (see Figure 8-27), which defines the **countercurrent exchanger (CCE)** model. Its main function is to **preserve** the **hyperosmolarity** of the **renal medulla.**

Kidney Endocrine Functions

The kidney performs four major endocrine functions:

- Secretion of erythropoietin (EPO).
- Formation of 1,25-dihydroxycholecalciferol.
- Production of renin.
- Production of prostaglandins.

CLINICAL CORRELATION

Systemic deficiency of EPO and consequent anemia often ensue as a result of chronic kidney disease (CKD), renal malignancy, or as an adverse effect of chemotherapy.

Erythropoietin

Erythropoietin (EPO) is glycoprotein hormone that stimulates RBC production in response to hypoxia. In healthy individuals, approximately 90% of all EPO is synthesized in the kidneys. EPO exerts its action through **EPO receptors (EpoR)** on the surface of **proerythroblasts** in the bone marrow. This accelerates the **maturation of proerythroblasts** (to their erythroblastic stage). In the absence of EPO, few RBCs are formed by the bone marrow. Therefore, individuals with insufficient concentrations of EPO (i.e., patients with severe kidney disease/failure), may become anemic, as they cannot appropriately respond to hypoxia by increasing EPO and RBC production.

KEY FACT

Human recombinant EPO is available as supportive treatment for patients with end-stage chronic renal failure (CRF), lifelong dialysis, HIV-associated anemia, and other similar conditions.

Remember: Patients must also receive proper iron supplementation.

Vitamin D: Formation of 1,25-Dihydroxycholecalciferol in the Kidneys

Vitamin D coupled with PTH provides the second most important mechanism regulating Ca^{2+} and phosphate metabolism. Vitamin D is stored in the **liver** in its **inactive** form, **25-OH-cholecalciferol**; its activation and action depend on the plasma Ca^{2+} concentration.

- Decreased **plasma Ca^{2+} levels** stimulate **PTH** secretion, which activates **1-α-hydroxylase** in the kidneys. This in turn enables the hydroxylation of 25-OH-cholecalciferol (C1 position) into **1,25-2OH-cholecalciferol** (physiologically **active form**), that acts simultaneously on the kidneys and small intestine to facilitate both Ca^{2+} and phosphate reabsorption.

KEY FACT

The action of 1,25-2OH-cholecalciferol in the kidney differs from that of PTH:

- **1,25-2OH-cholecalciferol** stimulates reabsorption of both Ca^{2+} and phosphate.
- **PTH** stimulates Ca^{2+} reabsorption, but inhibits phosphate reabsorption.

The syndrome of **vitamin D resistance** develops if the kidneys are unable to produce its active metabolite, **1,25-2OH-cholecalciferol,** despite normal vitamin D intake and availability. This condition can be either **inherited** (1α-hydroxylase deficiency) or **acquired** (chronic renal failure, CRF).

Prostaglandins

Vasodilate the **afferent arterioles** to **increase GRF**. Prostaglandins **PGE_2** and **PGI_2**, and **bradykinin** cause vasodilation, which in turn increases RBF and GRF. The use of NSAIDs inhibits prostaglandin production and their effects.

Hormones Acting on the Kidney

Just as the kidney produces several hormones, several more affect kidney function: atrial natriuretic factor, parathyroid hormone (PTH), aldosterone, angiotensin II, and ADH (see Table 8-9).

TABLE 8-9. Summary of Hormones Acting on the Kidney and Their Sites of Action

Hormone	Stimulus	Mechanism and Site of Action
ADH	▪ *Increased plasma osmolarity* ▪ Decreased blood volume	▪ ***Increases permeability of principle cells in collecting ducts.*** ▪ **Increases urea absorption in collecting ducts.** ▪ **Increases Na^+–K^+–$2Cl^-$ transporter in thick ascending limb.**
Aldosterone	▪ Decreased blood volume (via angiotensin II) ▪ Hyperkalemia	**Late distal tubule and collecting ducts:** ▪ *Increases Na^+ reabsorption.* ▪ Increases K^+ excretion. ▪ Increases H^+ excretion.
Angiotensin II	▪ Decreased blood volume (via renin)	▪ Contraction of **efferent arteriole** resulting in increased GFR.
ANF	▪ Increased atrial pressure	▪ Decreases Na^+ reabsorption; increases GFR.
PTH	▪ Decreased plasma Ca^{2+}	▪ Increases Ca^{2+} reabsorption. ▪ Decreases PO_4^- reabsorption. ▪ Increases 1,25(OH)2 vitamin D production.

Atrial Natriuretic Factor

The cardiac atria release atrial natriuretic factor (ANF) (a peptide) in response to increased stretching of the muscle fibers (secondary to volume overload or right heart failure). ANF causes vasodilation of the afferent arterioles, vasoconstriction of efferent arterioles, and decreased sodium reabsorption in the late distal tubules and collecting ducts. However, ANF will only cause small changes in BP (small increase in GFR), and its effects gradually decline within 24 hours despite the quantity of ANF secreted.

Parathyroid Hormone

PTH exerts two main actions on the kidneys:

- Inhibition of phosphate reabsorption in the PCT. This is accomplished by inhibition of the Na^+/phosphate co-transport. **Phosphaturia** is followed by increased cAMP excretion (**urinary cAMP**). This action of PTH on the kidney is important for the overall ECF Ca^{++} availability. Excess phosphate, resulting from decreased phosphate secretion leads to "trapping" (complexing) of the free Ca^{++}, thus, reducing its availability in the plasma.
- Stimulation of Ca^{++} reabsorption (**hypocalciuric action**) in the DCT. This occurs via the basolateral receptors, which employ the second messenger system i.e., conversion of AMP to cAMP. This further increases the availabitlity of free Ca^{++} in plasma (a tertiary resource following bone resorption and phosphaturia).

Renin-Angiotensin-Aldosterone System

The RAAS functions to allow the kidneys to regulate BP (see Figure 8-27). Renin is an enzyme synthesized and stored as an inactive compound, prorenin, in the juxtaglomerular cells of the kidneys (located in the walls of the afferent arterioles proximal to the glomeruli).

CLINICAL CORRELATION

Renal osteodystrophy results from **hyperphosphatemia** and **hypocalcemia,** both the result of little to no phosphate excretion by damaged kidneys, low vitamin D levels, and/or tertiary hyperparathyroidism.

CLINICAL CORRELATION

Na^+ and Ca^{++} reabsorption is **not coupled** at the level of the **distal tubule**. Therefore, use **thiazide diuretics** in cases of **idiopathic calciuria**—though they inhibit Na^+ reabsorption, they also act to increase reabsorption and prevent loss of Ca^{++} from the ECF.

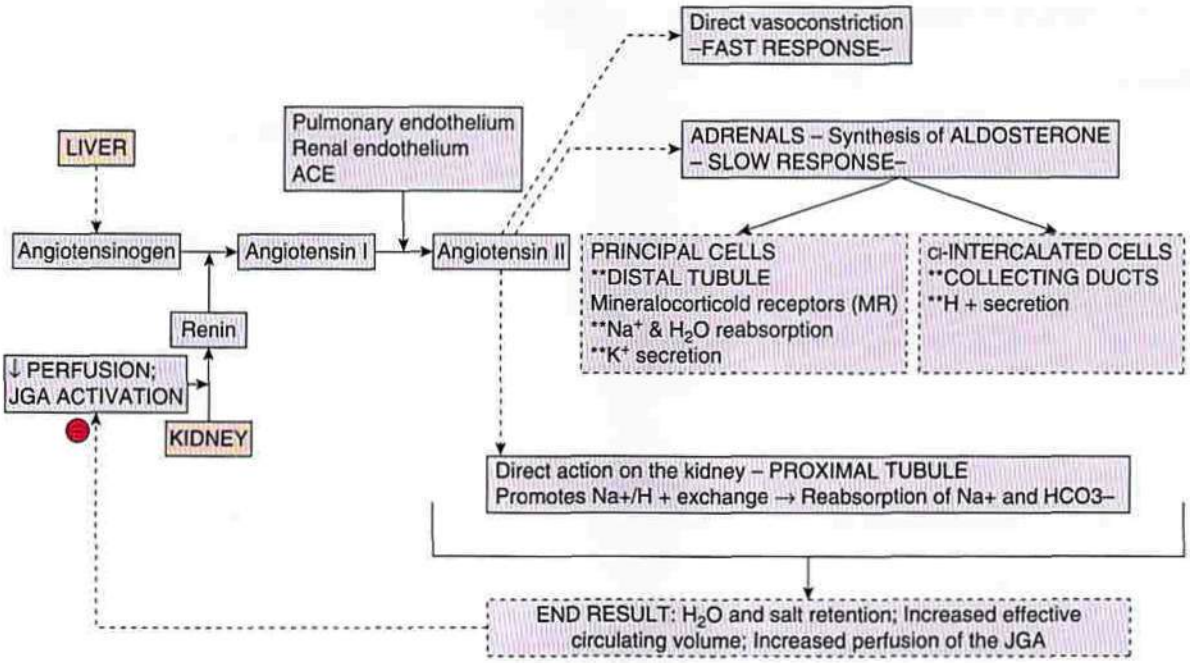


FIGURE 8-27. The rennin–angiotensin–aldosterone system (RAAS). JGA = juxtaglomerular apparatus.

FLASH BACK

- β_1 Agonists (e.g., isoproterenol) stimulate renin secretion.
- β_1 Antagonists (e.g., propranolol) inhibit renin secretion.

Several factors affect the **release of renin** into the bloodstream:

- Fall in arterial BP (hypotension), which results in decreased renal perfusion. This is perceived as a decreased stretch signal by the juxtaglomerular cells, which respond by excreting renin.
- Increased renal parasymphathetic activity.
- β_1 agonistic stimulation.
- Decreased Na^+ load/Na^+ delivery to the kidneys.

These conditions initiate the conversion of prorenin to renin in the juxtaglomerular cells, and its subsequent release into the bloodstream, where renin enzymatically cleaves angiotesinogen to release angiotensin I. **Angiotensin I** is then cleaved by angiotensin-converting enzyme (ACE), found in the endothelium of lung vessels and kidneys, to form **angiotensin II.**

There are at least three mechanisms by which circulating angiotensin II elevates arterial BP:

- **Direct vasoconstriction (fast response):** Constriction of the arterioles increases total peripheral resistance (TPR), and constriction of the veins promotes increased venous return of blood to the heart, both of which increase BP. The **efferent arterioles** of the kidney are especially affected.
- **Decreased excretion** of salt and water via stimulation of **aldosterone** synthesis **(slow response)** in the adrenal glands. Aldosterone promotes Na^+ reabsorption in the distal tubules and collecting ducts, which leads to increases in the ECF and blood volumes.
- **Direct action on the kidneys:** This action is independent of its actions via the aldosterone pathway. In this case, angiotensin II stimulates Na^+/H^+ exchange at the level of the proximal tubule, thus increasing the reabsorption of Na^+ and HCO_3^-.

Angiotensin II only persists in the blood for only 1 or 2 minutes before it is inactivated by angiotensinase. For this reason, the angiotensin II stimulation of aldosterone production is more influential in restoring arterial BP than are angiotensin's acute vasoconstrictive actions.

KEY FACT

Overall, angiotensin II serves to ↑ intravascular volume and ↑ BP.

Aldosterone

A mineralocorticoid synthesized in the zona glomerulosa of the adrenal cortex. While ACTH is the primary regulator of the corticosteroid hormones, aldosterone's synthesis and excretion are mainly regulated by **changes in ECF** via the renin-angiotensin system and changes in serum K^+ levels.

- **Late distal tubule:** Aldosterone exerts its action via stimulation of the mineralocorticoid receptors (**MRs**) on **principal cells.** This action increases the permeability of their apical (luminal) membrane to sodium and potassium by adding newly synthesized proteins (Na^+ channels; Na^+/K^+-ATPase and enzymes of the citric acid cycle), which stimulates ATP hydrolysis, reabsorption of Na^+ and water into the blood, and K^+ secretion into the urine.
- **Collecting duct:** Aldosterone also stimulates H^+ secretion by **α-intercalated** cells, thus regulating plasma HCO_3^- levels and acid–base balance.

FLASH BACK

MRs belong to the **group C: 3-ketosteroid receptors,** members of the nuclear receptor family that employs **ligand-activated intracellular transcription factors** to up- or downregulate the expression of genes in target cells.

Antidiuretic Hormone

Also known as **vasopressin**, ADH plays a major role in determining whether the kidney produces and excretes concentrated or dilute urine (see Figure 8-28). It originates in the posterior pituitary gland, and is produced in response to high serum osmolarity or significantly diminished blood volume. It is also produced in response to angiotensin II as part of the renin-angiotensin pathway, which acts to increase blood volume and BP.

KEY FACT

Mineralocorticoid escape is the ability of the glomerotubular autoregulatory mechanism to override the action of aldosterone in cases of increased ECF (volume expansion).

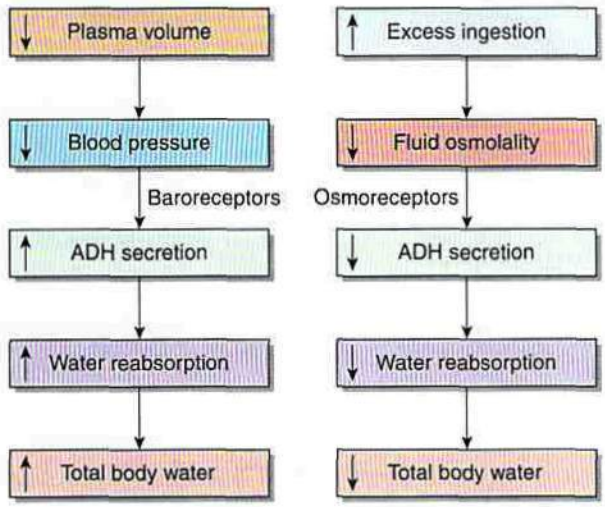


FIGURE 8-28. Regulation of water balance. The two major pathways for altering total body water: On the left, changes in ADH release from the anterior pituitary are triggered by changes in blood volume. On the right, decreased osmolality causes swelling of osmoreceptor cells in the anterior hypothalamus, which inhibits their firing and inhibits adjacent superoptic nuclei cells that reduces ADH secretion from their axonal extensions in the posterior pituitary. (Modified, with permission, from Eaton DC, Pooler JP, *Vander's Renal Physiology*, 6th ed. New York: McGraw-Hill, 2004: 123.)

- ADH acts on the **V2 receptors** on the **principal cells** in the **collecting ducts**. It causes an increase in the number of functioning water channels (**aquaporins**) thereby increasing permeability of the collecting ducts to water.
  - **Presence of ADH** leads to the passive reabsorption of large amounts of water in the collecting ducts, thus decreasing urine volume and increasing urine concentration (**hyperosmotic** urine).
  - In the **absence of ADH**, the collecting ducts are virtually impermeable to water, and large amounts of very dilute (**hyposmotic**) urine are excreted.
- In **high levels, ADH** also acts on **V1 receptors** on arterioles to cause vasoconstriction. This is particularly important in the setting of **hemorrhage, in which ADH helps maintain systemic BP.**
  - Decreased pressure leads to activation of the RAAS (see Figure 8-28), which raises total peripheral resistance and venous return.
  - Systemic baroreceptors (i.e., carotid sinus) sense decreased BP, which causes ADH release from the posterior pituitary gland. ADH acts on the kidneys to retain volume, and acts on systemic arterioles to maintain pressure.

CLINICAL CORRELATION

Syndrome of Inappropriate ADH secretion (SIADH) → excessively concentrated urine and inappropriately dilute serum → hyponatremia.

SIADH is most commonly caused by CNS disease or as a paraneoplastic syndrome.

Through these actions the kidneys retain fluid and systemic pressure is maintained, thereby counteracting hemorrhagic hypotension.

ACID-BASE HOMEOSTASIS

Acids and Bases

The body maintains serum pH within a tight range (approximately 7.40 ± 0.05) via a complex system that regulates acid production by metabolic processes. Importantly, most enzymes in the body function optimally within a very small pH range.

Acids

Exist as hydrogen ions containing a single free proton in the form of H^+. Molecules capable of releasing hydrogen ions into solution are known as **acids**.

- **Strong acids** rapidly dissociate into their ionic components in solution (e.g., $HCl \rightarrow H^+ + Cl^-$).
- **Weak acids** are less likely to rapidly dissociate as ionic components, and less readily release H^+. Carbonic acid (H_2CO_3) is an example of a weak acid.

Bases

Any ion or molecule that can **accept a hydrogen ion**. They usually have a net negative charge in solution.

- **Strong bases** readily and strongly accept hydrogen ions in solution, rapidly clearing the hydrogen ion concentration. For example, the hydroxide ion (OH^-) is a strong base.
- **Weak bases** less readily accept hydrogen ions, resulting in a much weaker interaction than that of a strong base. Bicarbonate (HCO_3^-) is an example of a weak base.

Buffers

Ionic compounds that resist changes in pH when acid is either added or removed. Buffers function along a titration curve and are most effective along the linear portion of the curve (±1.0 pH unit from the pK_a value for that par-

ticular buffer). Buffer–acid interactions may be calculated using the **Henderson-Hasselbalch equation.**

$$pH = pK_a + \log [A^-]/[HA]$$

where **A^- is the base form of buffer and HA is the acid form of buffer.**

Acid Production

Acid production within the body is of two types, **volatile and non-volatile.** Most of the acids in the body are weak acids, with the exception of hydrochloric acid (HCl^-), secreted in the form of gastric acid.

Volatile Acid

Produced in the form of CO_2 via cellular metabolism. The CO_2 produced then reacts with H_2O via the enzyme carbonic anhydrase to produce the reaction below:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Nonvolatile Acid

The product of protein catabolism in the form of sulfuric acid and phospholipid catabolism in the form of phosphoric acid. Other nonvolatile acids produced by the body include salicylic acid, lactic acid, and ketones.

Physiologic Buffers

The body has several molecules that act as a buffer system. These are categorized based on their location in relation to the cellular membrane: **intracellular** and **extracellular.**

Intracellular Buffers

Consist of proteins and organic phosphates.

- **Proteins:** Certain chemical compounds in amino acids, such as alpha-amino groups and imidazole groups, have pH values within the physiologic pH range and are, therefore able to act as buffers due to their net negative value. Hemoglobin is also an intracellular buffer.
- **Organic phosphates:** These include metabolic substrates including AMP, ADP, ATP, and 2-3-diphosphoglycerate.

Extracellular Buffers

Consist of HCO_3^- and phosphates.

- **Major:** HCO_3^- is the major extracellular buffer. It is produced via a reaction catalyzed by carbonic anhydrase.
- **Minor:** Phosphate is the minor extracellular buffer. Its most important function is as a buffer of urine.

Acid-Base Homeostasis

The body uses chemical buffer systems to regulate acid–base homeostasis.

Buffer Systems

Consist of a pair of substances, a **weak acid** and **weak base** that undergo a reversible chemical reaction. The weak acid yields free H^+ as the hydrogen

ion concentration [H^+] starts to fall, while the weak base can bind with the free H^+ when [H^+] starts to rise.

The **Henderson-Hasselbalch** equation describes the relationship between [H^+] and the members of a buffer pair. This equation fits the titration curve for all weak acids.

$$pH = pK_a + \log \frac{\text{proton acceptor}}{\text{proton donor}} = pK_a + \log \frac{[A^-]}{[H^+]}$$

Stated in terms that describe the **blood bicarbonate buffer**:

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03\ P_{CO_2}}$$

The major chemical buffer system that the body uses to regulate extracellular acid-base balance is the carbonic acid/bicarbonate buffer system. It is expressed as the **carbonic anhydrase reaction**:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

This is a reversible equilibrium reaction. The body regulates hydrogen ion concentration via CO_2 and HCO_3^- concentrations in the blood. The kidneys and lungs are the principal organs responsible for regulation of acid–base homeostasis.

Physiologic pH

Normal blood pH is 7.4, and may range from 7.35 to 7.45. Values beyond the levels of 6.8–8.0 are nearly incompatible with life due to changes in enzymatic function and protein denaturation.

- **Acidemia** vs **acidosis:**
  - **Acidemia** is a nonspecific term describing an increase in hydrogen ion concentration in the blood, and is applicable when pH falls below normal (< 7.35).
  - **Acidosis** describes specific metabolic derangement responsible for pH changes (e.g., metabolic acidosis).
- **Alkalemia** vs **alkalosis:**
  - **Alkalemia**: Decrease in hydrogen ions or increase in bicarbonate ions that raises the pH above normal levels (> 7.45).
  - **Alkalosis** describes the specific metabolic derangement responsible for pH changes.

Acid-Base Homeostasis: The Kidney

Through a variety of mechanisms, the kidney is the primary regulator of H^+ and HCO_3^- in the serum. Since renal compensation occurs through chemical buffers under hormonal control, serum changes in pH and clinical symptoms become evident relatively slowly (i.e., over hours to days).

- **Renal production of H^+ and HCO_3^-: Proximal and distal tubule cells** contain intracellular carbonic anhydrase that produces H^+ and HCO_3^- from CO_2 and H_2O via the intermediate of H_2CO_3.
- **Secretion of H^+:** The hydrogen ion may be secreted in **two forms**: Titratable acid ($H_2PO_4^-$) and ammonium (NH_4^+).

- **Secretion as $H_2PO_4^-$:** Excretion of H^+ as titratable acid depends on the amount of urinary buffer (phosphate) present, as well as the pK of that buffer. Once H^+ is secreted, it combines with HPO_4^{2-}, resulting in a net secretion of H^+ ions. This accounts for the pH of urine being lower than that of serum, approximately 4.5.
- **Secretion as NH_4^+:** This mechanism depends on the amount of ammonia synthesized (from glutamine) by renal cells. Secretion of NH_3 depends largely on urine pH. The lower the pH, the greater secretion of H^+ and NH_3 as NH_4^+. In states of **acidosis** there is a compensatory increase in this process in order to increase H^+ secretion.
- **Reabsorption of HCO_3^-:** Reabsorption of bicarbonate is regulated by increased P_{CO_2}, as well as angiotensin II, which stimulates the Na+-H+ exchange pump. This in turn leads to an increase in bicarbonate reabsorption and eventual contraction alkalosis. Increased ECF volume causes decreased HCO_3^- reabsorption and **dilutional acidosis**, while decreased ECF volume results in increased HCO_3^- reabsorption (**contraction alkalosis**).

Acid-Base Homeostasis: The Lungs

The lung is also a primary regulator of acid-base homeostasis. While altered ventilatory states may be responsible for primary derangements, they may also compensate for primary metabolic derangements. Because respiration is an open gas system (that is, the serum concentration of dissolved CO_2 is kept constant by altering the ventilatory rate), compensation takes place through gas exchange. Compensatory changes in ventilatory rate can be seen within minutes.

- **Compensation states:** Metabolic processes resulting in of bicarbonate concentration derangement, will be followed by a compensatory change respiratory rate, and thus in carbon dioxide concentration.
  - **Metabolic alkalosis** (increased HCO_3^-) → **decreased respiratory rate**, promoting retention of CO_2 and an increase in pH.
  - **Metabolic acidosis** (a loss of HCO_3^-) → **increased respiratory rate**, decreased CO_2, and a decrease in pH.
- **Derangement states:** The lungs may also be the primary cause of either a respiratory alkalosis or acidosis.

Metabolic Acidosis/Alkalosis

Metabolic Acidosis

Occurs secondary to either a loss of bicarbonate or an excess of acid. Conditions that lead to metabolic acidosis can be differentiated based on the **anion gap**, defined as:

$$[Na^+ - (HCO_3^- + Cl^-)] \text{ (normal = 10–12)}$$

Metabolic Alkalosis

Occurs secondary to either a loss of acid or excess of base:

- Emesis
- Hyperaldosteronism
- Diuretics (loop and thiazide) "contraction alkalosis"
- Laxative abuse
- Hypercalcemia/milk-alkali syndrome
- Hypokalemia



MNEMONIC

Anion gap acidosis: **MUDPILES** and non-gap acidosis: **HARDUP.**

High anion gap	Normal anion gap
Methanol	**H**yperalimentation
Uremia	**A**cetazolamide
Diabetic ketoacidosis	**R**enal tubular acidosis
Phenformin, Paraldehyde	**D**iarrhea
Isoniazid, Infection, Iron	**U**reteroenteric shunt
Lactic acidosis	**P**ancreatic fistula
Ethylene glycol, **E**thanol	
Salicylates	

Respiratory Acidosis/Alkalosis

Respiratory Acidosis

Occurs secondary to retention of CO_2. This can result from conditions that inhibit the medullary respiratory center (decreased respiratory drive), weakening or paralysis of the muscles of respiration, or decreased CO_2 exchange (see Table 8-10).

Respiratory Alkalosis

Occurs due to low-plasma concentrations of CO_2. This can result from conditions that affect the CNS, the respiratory system, or from iatrogenic causes (see Table 8-11).

KEY FACT

In primary respiratory acid–base disorders, deflection of pH and P_{CO_2} occur in **opposite** directions.

Acid-Base Clinical Implications

The key points when approaching a clinical scenario involving an acid-base disturbance (see Table 8-12) are the following:

- The lungs regulate the concentration of P_{CO_2}.
- Kidneys regulate concentration of HCO_3.
- Compensation is never complete (i.e., pH never returns to 7.40).

CLINICAL CORRELATION

Acidemia (pH < 7.40) produced by a primary respiratory acidosis results in P_{CO_2} > 40 mmHg.

Acidemia produced by a primary metabolic acidosis results in P_{CO_2} < 40 mmHg.

The next step in analysis is to determine whether **the response is an acute or chronic process:**

- The answer lies in the normality of the pH relative to the derangement in P_{CO_2}.
- To achieve this, sufficient time must pass to allow the kidney to compensate for the primary disorder (i.e., hypocapnia) by excreting, or retaining, bicarbonate.
- Chronically, for every **drop of 10 mmHg in P_{CO_2}, we expect a compensatory reduction in bicarbonate of about 5 mmol/L.**
- If the compensation is not appropriate, there must be another process occurring simultaneously. That is, a **mixed acid-base disorder** exists.

TABLE 8-10. Causes of Respiratory Acidosis

Mechanism	Causes
Inhibition of medullary respiratory center	Drugs (opiates, sedatives, anesthetics) CNS tumors/trauma CNS hypoxia Hypoventilation of obesity, Pickwickian syndrome
Weakening or paralysis of muscles of respiration	Guillain-Barré syndrome Myasthenia gravis Toxins (botulinum toxin, organophosphates) Muscle relaxants Scoliosis, certain myopathies, muscular dystrophy
Decreased CO_2 exchange	Chronic obstructive pulmonary disease Acute respiratory distress syndrome

TABLE 8-11. Causes of Respiratory Alkalosis

Mechanism	Causes
Central	▪ Head trauma ▪ Stroke ▪ Anxiety, stress, hyperventilation ▪ Drugs (salicylate intoxication) ▪ Certain endogenous compounds (e.g., progesterone in pregnancy)
Pulmonary	▪ Pulmonary embolism ▪ Asthma ▪ Pneumonia
Iatrogenic	▪ Increased respiratory rate while on controlled ventilation

Signs of mixed disorders include:

- Marked increase in pH with little change in P_{CO_2} and $[HCO_3^-]$.
- Marked increase in P_{CO_2} and $[HCO_3^-]$ with little change in pH, implying offsetting abnormalities.

If a **mixed disorder** is suspected, then calculate the anion gap and determine whether an excess exists. A simplified analysis of the excess anion gap (also called **delta-delta analysis**) is shown below.

$$\Delta\text{Anion gap (AG)} = \text{Calculated AG} - 12$$

$$\Delta\,[HCO_3^-] = 24 - \text{Measured}\,[HCO_3^-]$$

TABLE 8-12. Summary of Primary Acid–Base Disturbances

Disorder	P_{CO_2}	+	H_2O	↔	H^+	+	HCO_3^-	Respiratory Compensation	Renal Compensation
Metabolic acidosis	↓				↑		⇓	Hyperventilation	↑ $[H^+]$ excretion ↑ $[HCO_3^-]$ up
Metabolic alkalosis	↑				↓		⇑	Hypoventilation	↑ $[HCO_3^-]$ excretion
Respiratory acidosis	⇑				↑		↑[a]	None	↑ $[H^+]$ excretion ↑ $[HCO_3^-]$ up
Respiratory alkalosis	⇓				↓		↓	None	↓ $[H^+]$ excretion ↓ $[HCO_3^-]$ up

⇑ or ⇓ = Primary disturbance.

↑ or ↓ = Effect of primary disturbance or compensation.

[a]May be unchanged or slightly lower according to the Henderson-Hasselbalch equation:
$pH = 6.1 + \log [HCO_3^-]/[CO_2]$ Normal $[HCO_3]/[CO_2] = 20$.

Compare the two:

- Δ AG > Δ [HCO_3^-] = Metabolic alkalosis + Metabolic acidosis
- Δ AG < Δ [HCO_3^-] = Wide AG + Non-AG metabolic acidosis
- ~Equal? = Wide anion gap metabolic acidosis

No anion gap implies non-anion gap metabolic acidosis (also known as hyperchloremic acidosis). Intuitively, if there is metabolic acidosis with no anion gap, the only serum anion that can be causing it is chlorine.

This analytical thought process is depicted in Figure 8-29.

Acid-Base Nomogram

The nomogram is a quick reference tool that can be used during clinical rotations (see Figure 8-30).

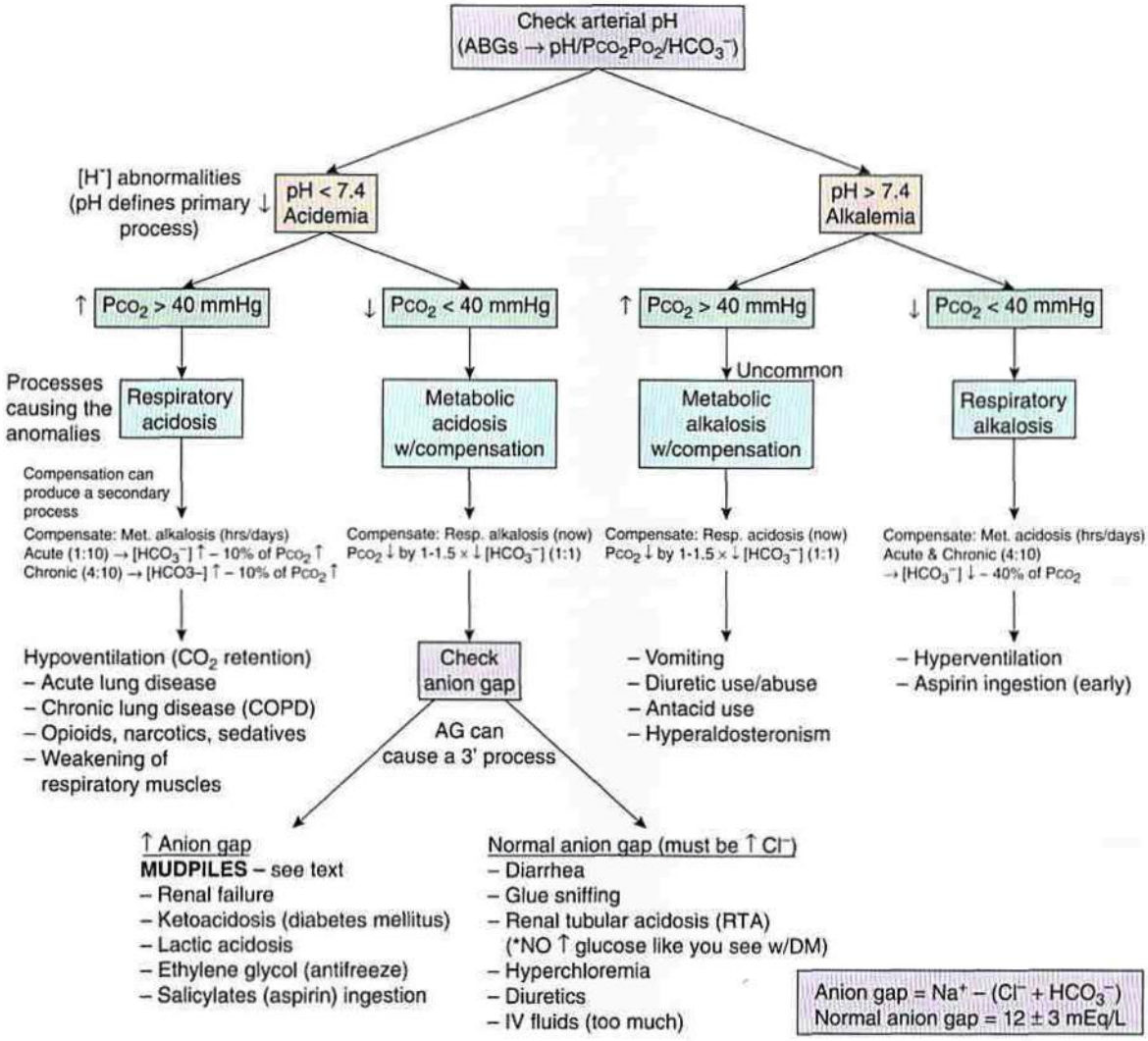


FIGURE 8-29. Flowchart describing simplified acid-base analysis.

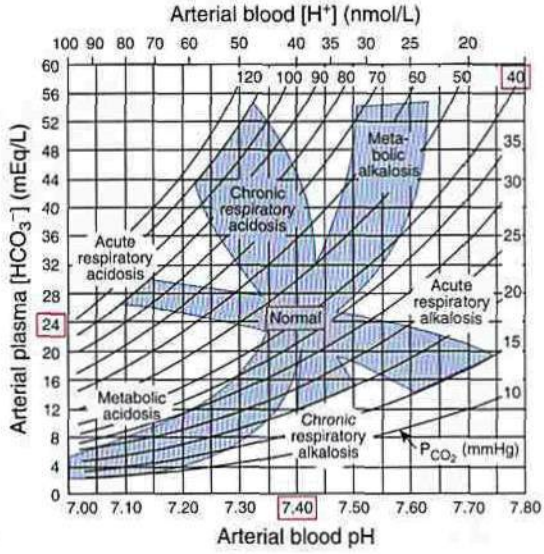


FIGURE 8-30. Acid-base (Davenport) nomogram. Note that the center of the diagram is detailed in Figure 8-31. (Modified, with permission, from Ganong WF, *Review of Medical Physiology*, 22nd ed, New York: McGraw-Hill, 2005: 734.)

While the acid-base nomogram is an indispensable clinical tool, it is practically impossible to memorize for test purposes. Figure 8-31 provides a simplified version depicting the **center of the nomogram**. Knowing this basic setup answers the simple acid-base problems very quickly. It also helps to narrow down your answers if you do not know where to start with a more complicated mixed disorder. (See Table 8-13.)

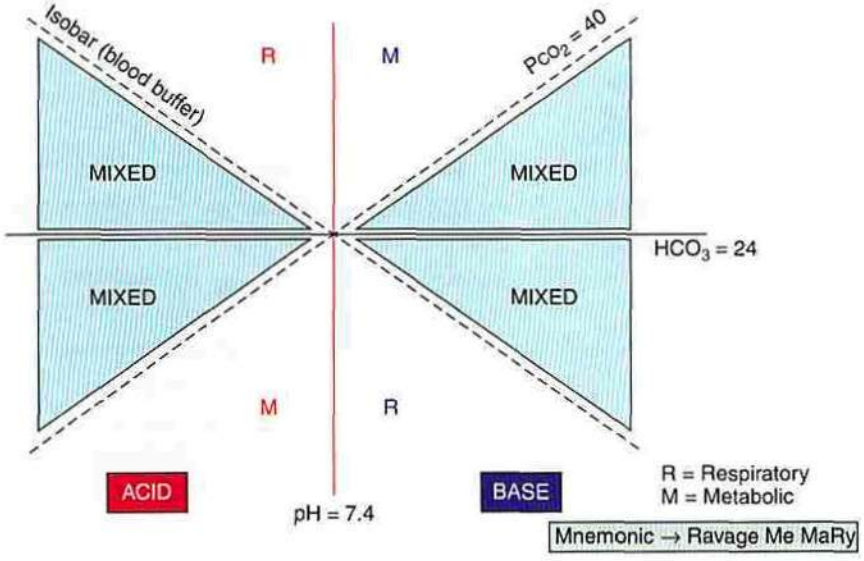


FIGURE 8-31. Center of the Davenport acid-base nomogram, simplified approach. To read this chart: Compensation is always toward the middle (i.e., back to normal: pH = 7.4, HCO_3 = 24, P_{CO_2} = 40.) Upper left quadrant (R) = respiratory acidosis; bottom left quadrant (M) = metabolic acidosis; upper right quadrant (R) = metabolic alkalosis; bottom right quadrant (M) = respiratory alkalosis. Everything in the middle quadrants = mixed respiratory/metabolic.

TABLE 8-13. Sample Problems

Sample problem 1:

A 21-year-old male medical student presents to the infirmary with a 2-day history of nausea and vomiting. His temperature is 100.4° F, BP is 100/60 mmHg supine and 80/50 mmHg sitting, and pulse is 100/min supine and 130/min sitting. His examination is otherwise unremarkable. Serum electrolytes are: Na = 134 mEq/L; K = 3.2 mEq/L; Cl = 90 mEq/L; and HCO_3 = 32 mEq/L. Urine electrolytes are Na < 10 mEq/L and Cl < 10 mEq/L. An arterial blood gas shows pH 7.47, Pco_2 45 mmHg; and Po_2 98 mmHg. What acid–base disturbance is present?

a. Chronic respiratory acidosis.
b. Metabolic alkalosis.
c. Mixed non-anion gap metabolic acidosis and metabolic alkalosis.
d. Mixed respiratory acidosis and metabolic alkalosis.
e. Mixed respiratory acidosis, non-anion gap metabolic acidosis, and metabolic alkalosis.

Answer: (b) Metabolic alkalosis.

Clinically, the scenario is consistent with a metabolic disturbance caused by loss of acid. Laboratory values should confirm what we already suspect. Applying our analytical approach, the minimum diagnosis has to be metabolic alkalosis based on alkalemic pH and concurrent hypercarbia (pH and Pco_2 are both increased).

Next, is the compensation appropriate? For every 10-mmol/L rise in plasma bicarbonate, Pco_2 should rise by 6 mmHg. In this case, the bicarbonate is up 8 mmol/L and the Pco_2 is up 5 mmHg, which is appropriate. The anion gap is 12, which is normal.

Sample problem 2:

A 20-year-old African American woman presents to your emergency room with new-onset type 1 DM (DM-1) accompanied by a 3-day history of anorexia, nausea, and vomiting. Her vitals include temperature 100°F, BP 98/60 mmHg supine and 80/50 mmHg sitting, pulse 90/min supine and 130/min sitting, and respirations are 24/min. Urinalysis shows 4+ glucose and ketones. Serum electrolytes are: Na = 136 mEq/L, K = 5.3 mEq/L, Cl = 94 mEq/L, and HCO_3 = 14 mEq/L. Serum glucose = 424 mg/dL and BUN = 30 mg/dL, and creatinine =1.0 mg/dL. Arterial blood gases show pH 7.32, Pco_2 28 mmHg, and Po_2 is 98 mmHg. What acid–base disturbance is present?

a. Chronic respiratory alkalosis.
b. Wide anion gap metabolic acidosis.
c. Mixed anion gap metabolic acidosis and metabolic alkalosis.
d. Mixed respiratory alkalosis and wide anion gap metabolic acidosis.

Answer: (c) Mixed anion gap metabolic acidosis and metabolic alkalosis.

Clinically, one should suspect a mixed disorder based on the time course. Applying our analytical approach, the minimum diagnosis of metabolic acidosis is based on acidemia (pH < 7.4) with concurrent low Pco_2. Next, to determine whether the compensation is appropriate, the rule is $Pco_2 = 1.5 \times [HCO_3] + 8 + 2$. In this case, the observed value of Pco_2 = 28 is appropriate. Next, we want to explain the metabolic component. Calculating the anion gap as [sodium] – ([chloride] + [bicarbonate]) produces a value of 28 in this case, well above the normal of 12. So, we have at least a wide anion gap metabolic acidosis. We then have to compare the "delta" anion gap with the "delta" bicarbonate concentration. In a simple wide anion gap acidosis, "delta" gap = "delta" bicarb. Here, however, "delta" gap = 28 (observed) – 12 (normal) = 16. "Delta" bicarb = 24 (normal) – 14 (observed) = 10. Since "delta" gap is greater than "delta" bicarb, there has to be concurrent metabolic alkalosis. These conclusions are consistent with the clinical picture of plasma volume contraction and vomiting.

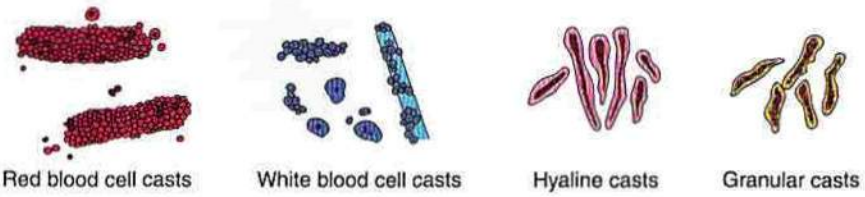


FIGURE 8-32. Morphology of renal casts.

Pathology

URINARY CASTS

Casts seen on urinalysis can be an indication of tubular pathology (see Figure 8-32). Cells within the casts reveal an intrarenal source. Other casts such as **hyaline casts** are seen in normal individuals, but are also seen in low-intravascular states. All casts are made of a protein matrix primarily composed of **Tamm–Horsfall mucoprotein** (see Table 8-14).

KEY FACT

Presence of casts indicates that hematuria or pyuria is of renal origin.

GLOMERULOPATHIES

The term **glomerulopathies** applies to a group of conditions that affect the glomeruli. These entities are divided into two major groups (see Table 8-15), based on their pathogenesis and clinical manifestations.

FLASH BACK

Type II hypersensitivity: Anti-GBM diseases; linear deposits of IgG along the GBM; Consider Goodpasture's and type I rapidly progressive glomerulonephritis (RPGN).

NEPHROTIC SYNDROME

This condition results from an **increased permeability** of the GBM, secondary to various intra- and extrarenal insults. The intact GBM is negatively charged, thus preventing filtration of proteins in urine. In **nephrotic** syndrome, however, the charge is lost, which accounts for the **loss of plasma proteins** (predominantly the low-molecular-weight **albumin**) in the urine.

FLASH BACK

Type III hypersensitivity: Granular deposits of IgG-antibody-complement; consider poststreptococcal and type II RPGN and membranous glomerulopathy.

TABLE 8-14. Urinary Casts

Casts	Causes	Findings
Epithelial cell casts	ATN, ethylene glycol toxicity, heavy metal poisoning, acute rejection of transplant graft.	Desquamated tubular cells in a protein matrix.
RBC casts	Glomerulonephritis: IgA nephropathy, poststreptococcal glomerulonephritis, and Goodpasture's syndrome. Malignant hypertension. Vasculitis. Renal ischemia.	Clumps of RBCs indicating RBCs are of glomerular origin versus bladder origin (e.g., bladder cancer).
WBC casts	Pyelonephritis. Interstitial nephritis. Lupus nephritis.	Clumps of WBCs. **WBC casts** indicate inflammation in renal interstitium, tubules, and glomeruli. **WBCs** in urine indicate acute cystitis.
Hyaline casts	Often seen in normal urine. Pyelonephritis.	Glassy looking. Composed of **Tamm–Horsfall protein.**
Granular casts	Severe renal disease. Nephrotic syndrome.	Derived from renal tubular cells.
Fatty casts	Nephrotic syndrome.	Fat droplets in hyaline matrix. **Maltese-cross configuration.**

TABLE 8-15. General Division of Glomerular Diseases

Conditions That Manifest With Nephrotic Syndrome (Increased GBM Permeability)	Conditions That Manifest With Nephritic Syndrome (Inflammatory Damage to the Glomeruli)
Minimal change disease	Acute proliferative glomerulonephritis (poststreptoccocal/infectious).
Focal segmental glomerulosclerosis	Rapidly progressive glomerulonephritis (RPGN, crescentic).
Membranous glomerulopathy	Anti-GBM disease. Goodpasture's syndrome.
MPGN[a]	MPGN[a].
Diabetic nephropathy associated with multisystemic disease	IgA nephropathy (Berger's disease).
Renal amyloidosis associated with multisystemic disease	Hereditary nephritis (Alport's syndrome).

[a]MPGN can present as either nephrotic or nephritic syndrome.

KEY FACT

High ratio of low- to high-MW proteins (albumin to globulin) indicates **highly selective proteinuria,** with albumin and transferrin in the urine.

CLINICAL CORRELATION

The excess fluid in the body may take several forms:

- Puffiness around the eyes, characteristically in the morning.
- Pitting edema over the legs.
- Pleural effusion.
- Ascites.

KEY FACT

Proteinuria (> 3.5 g/24 h), hypoalbuminemia, edema, hyperlipidemia, and hypercoagulation are the hallmarks of nephrotic syndrome.

FLASH BACK

Patients with nephrotic syndrome are at increased risk of infection with staphylococci and pneumococci.

Nephrotic syndrome is characterized by a complex of secondary metabolic changes that are characteristic for nephrotic syndrome:

- **Massive proteinuria** (> 3.5 g/24 h).
- **Hypoalbuminemia** (plasma albumin level < 3 g/dL) develops secondary to the proteinuria. Albumin accounts for ~ 60% of total human plasma proteins and is the main mediator of the **serum oncotic pressure.** Therefore, massive loss of albumin sets the stage for development of edema.
- **Edema** starts to develop as a result of lowered oncotic pressure, which leads to loss of fluid from the circulation into the interstitial space. Decreased intravascular volume further leads to activation of the RAAS, sympathetic activation, release of vasopressin, and decreased atrial natriuretic peptide. All of these changes result in increased renal electrolyte and water retention, thus adding to the edema.
- **Hyperlipidemia** and consecutive **lipiduria** result from an increased production of serum proteins by the liver in an attempt to maintain (increase) the oncotic pressure. However, the liver is not able to synthesize sufficient quantities of lipoproteins in order to successfully counteract the edema or hypoalbuminemia.
- **Hypercoagulability** secondary to the loss of anticoagulant factors through the damaged glomeruli.

There are different pathologies that result in a clinical presentation of nephrotic syndrome. The definitive diagnosis can only be made with a renal biopsy. However, each of the following disorders has associated symptoms and time courses that help to guide diagnosis and treatment.

Minimal Change Disease

Minimal change disease is the **most frequent cause** of nephrotic syndrome in **children** (over 80% of cases; seen in those aged 2–3 years). It is so named due

to the normal appearance of the glomeruli observed under **light microscopy**, while **electron microscopy** shows loss (**effacement**) of the visceral epithelial foot processes, thus causing increased glomerular permeability.

- Proximal tubules are often heavily laden with lipids secondary to increased tubular reabsorption of lipoproteins passing through the injured glomeruli, hence the old name **"lipoid nephrosis."**

Presentation

Patients with this disorder will most frequently be children between the ages of 2 and 3 years. Symptoms manifest as an insidious onset of nephrotic syndrome without any other obvious clinical disease (no hypertension). The **proteinuria** is termed **"selective"** because primarily albumin is lost. Renal function is normally maintained, with only a slight decline in GFR in 10%–30% of patients.

Diagnosis

As with all glomerulopathies, diagnosis is dependent on renal biopsy.

- **Light microscope** (see Figure 8-33): No obvious morphologic changes are seen in the glomeruli, other than the lipoid appearance of the cells in the proximal tubules **(lipoid nephrosis).**
- **Electron microscope: Effacement** of visceral epithelial foot processes and increased lipoproteins in the PCTs.

Definitive diagnosis of minimal change disease can only be made when nephrotic syndrome is associated with glomeruli showing diffuse loss of foot processes on electron microscopy.

Treatment

Initial therapy includes **high-dose oral glucocorticoids (prednisone)** for up to 8 weeks. For those that fail to achieve lasting remission (defined as either relapse during steroid therapy, or recurrence more than three times per year after the steroid taper), **alkylating agents** such as cyclophosphamide or chlorambucil have been shown to be effective.

Prognosis

In children, prognosis is excellent, with 90% of cases responding to treatment. In adults, prognosis is not as good, with only 50% responding to treatment.

KEY FACT

Minimal change disease is also known as **lipoid nephrosis, nil disease,** or **foot process disease.**

KEY FACT

Foot process effacement is not unique to minimal change disease. It can also be seen in other proteinuric diseases.

KEY FACT

Minimal change disease is the **most common cause of childhood nephrotic syndrome.** Responds well to steroids.

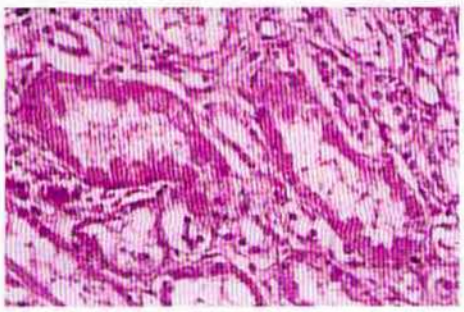


FIGURE 8-33. Histology of minimal change disease (lipoid nephrosis). Note the foamy (or granular) appearance of the cells of the proximal tubules due to reabsorption of lipoproteins leaking through diseased glomeruli. (Courtesy of Uniformed Services University of the Health Sciences.)

Focal Segmental Glomerulosclerosis

KEY FACT

FSGS is more severe in HIV-positive patients.

KEY FACT

Children with minimal change disease = Selective proteinuria.
Children with focal segmental glomerulosclerosis = Nonselective proteinuria; higher incidence of hematuria and hypertension.

Focal segmental glomerulosclerosis (FSGS) is considered to be a more severe form of minimal change disease due to the similar loss of visceral epithelial foot processes. The pathologic lesion is sclerosis of < 50% of glomeruli of a tissue section (hence the name **focal**) with the sclerosis involving only distinct portions of the affected glomeruli (hence the name **segmental**). The cause is still unknown. This disease accounts for about 33% of nephrotic syndrome in adults and 50% of cases in African Americans.

Presentation

Patients present with nephrotic syndrome. Unlike in minimal change disease, patients will have **nonselective proteinuria** as well as **hypertension**, mild hematuria, and possibly decreased renal function. This disorder is associated with HIV and heroin use.

Diagnosis

Definitive diagnosis is based on renal biopsy.

- **Light microscope**: Two distinct features are notable: **focal** (hyaline masses) and **segmental** sclerosis. Proper tissue sample biopsy is important because the prognosis of this disorder is worse than that of minimal change disease. In addition, proper diagnosis will determine the appropriate course of treatment.

Treatment

Unlike with minimal change disease, only 20%–40% of patients will undergo remission when treated with **oral glucocorticoids**. If there is no remission of proteinuria with steroids, **cyclophosphamide** and **cyclosporine** can be used at doses similar to those for minimal change disease.

Prognosis

Generally poor, with approximately 50% of patients with this disorder developing end-stage renal disease (ESRD) within 10 years. Even following renal transplantation, there is a great risk of disease recurrence.

Membranous Glomerulopathy

KEY FACT

Common cause of nephrotic syndrome in adults; nonselective proteinuria.

The pathogenesis of membranous glomerulopathy is not clearly established. However, immunofluorescent studies have led to a hypothesis of immune complex deposition, which is supported by its association with certain infections and systemic diseases. It is the **leading cause of nephrotic syndrome in adults**, accounting for 30%–40% of cases and less than 5% of cases in children. Peak incidence is from ages 30–50 and it is seen predominantly in men (2:1 ratio).

Presentation

Insidious onset of **nephrotic syndrome** in otherwise healthy patients. Membranous glomerulopathy occurs in association with systemic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), as well as infections, such as hepatitis B and C, syphilis, schistosomiasis, malaria, and leprosy. Previous use of gold or penicillamine is associated with this disorder.

Diagnosis

Based on renal biopsy.

- **Light microscope**: Diffuse GBM thickening due to subepithelial deposits nestled against the GBM.
- **Electron microscope**: Subepithelial deposits in a **"spike"** (extensions of GBM around deposits) and **"dome"** (deposits in the GBM) pattern. The deposits have been shown to be IgG and C3 using immunofluorescent staining.

Treatment

Use of oral glucocorticoids does not result in any improvement in symptoms. Cyclophosphamide and cyclosporine reduce proteinuria and slow the decline of GFR. Transplantation has been shown to be effective for patients that progress to ESRD.

Prognosis

Remission is spontaneous in 40% of patients with 30%–40% developing a chronic clinical picture with frequent relapses. The remaining 10%–20% will go on to develop ESRD in 10–15 years.

Membranoproliferative Glomerulonephritis

The pathogenesis of membranoproliferative glomerulonephritis (MPGN) is unknown. There are two distinct types:

- **Type I** (**two-thirds** of cases): Suspected to be secondary to immune complex formation (type III hypersensitivity), which is supported by the association with certain infections such as hepatitis B and C. Some cases may be associated with **nephritic presentation.**
- **Type II** (**one-third** of cases): Unknown pathogenesis; often associated with the C3 nephritic factor (C3NeF). It is also called **dense deposit disease,** due to a dense deposition of an unknown substance between the lamina densa and subendothelial space of the GBM. While C3 is present, there are **no IgG** deposits.

FLASH BACK

C3NeF is a C3-convertase-specific autoantibody, which prevents its degradation and causes incessant C3 activation.

Presentation

Patients with **type I** tend to present with **nephrotic** syndrome, while patients with **type II** can present with **either** nephrotic or nephritic syndrome, or a mix of the two. Type I is associated with hepatitis B and C, SLE, and systemic infections with large amounts of immune complex formation (i.e., bacterial endocarditis and sepsis, among others).

Diagnosis

Diagnosis is based on clinical presentation and renal biopsy. The disorder is characterized on tissue section by thickening of the GBM and proliferation of mesangial cells.

- **Electron microscopy**: Generally the GBM appears to be divided by an electron-dense material.
  - **Type I** shows subendothilial, **electron-dense deposits** of IgG and C3.
  - **Type II** shows intramembranous deposits and increased size of glomeruli, as well as increased cellularity of the mesangial cells. The capillary wall often shows a double contour, or **tram-track appearance,** as a result of **GBM splitting.**

KEY FACT

MPGN = Tram-track appearance on electron microscopy and subendothelial humps.

Differentiation between types I and II is important due to differences in prognosis.

KEY FACT

Sustained C3 activation results in very low C3 levels, which is an important diagnostic feature.

Treatment

There is no effective therapy for this disease.

Prognosis

Differs between types I and II.

- **Type I** has a relatively benign course, with 70%–85% of patients having no chronic decline in GFR.
- **Type II** tends to have a worse prognosis, with deteriorating GFR. A majority of patients progress to ESRD after 5–10 years.

NEPHROPATHIES ASSOCIATED WITH SYSTEMIC DISORDERS

Many systemic disorders ultimately affect the kidneys. Specific entities associated with nephrotic syndrome include diabetic nephropathy, renal amyloidosis, and lupus nephritis.

Diabetic Nephropathy

Diabetic nephropathy is the leading cause of ESRD in Western society, secondary to glomerular hypertension and hyperfiltration. The **first sign** of injury to the glomerulus is **microalbuminuria**, which occurs about 5–10 years before other symptoms develop (see Figure 8-34). If untreated, microalbuminuria slowly progresses to nephrotic-range proteinuria. Nephropathy occurs in ~ 30% of cases of DM-1 and ~ 20% of cases of DM-2.

Presentation

Typically, CRF aggravated by glomerulosclerosis will lead to fluid filtration abnormalities and a full spectrum of other disorders of kidney function. Cardinal symptoms include **hypertension** and **edema** (as a result of fluid retention). Other complications may include **arteriosclerosis** of the **renal artery** and the **efferent** arterioles. If left untreated, **nephrotic-range proteinuria** will ultimately develop.

KEY FACT

Hyaline arteriolosclerosis is a hallmark of DM; efferent arterioles are affected before afferent arterioles.

During its early course, diabetic nephropathy has virtually no symptoms. Late-stage diabetic nephropathy will manifest as full blown CRF.

Diagnosis

Usually diagnosed on clinical grounds without the need for a renal biopsy. Should be suspected in patients with either DM-1 or DM-2 who have already developed retinopathy and neuropathy and have dipstick-positive proteinuria.

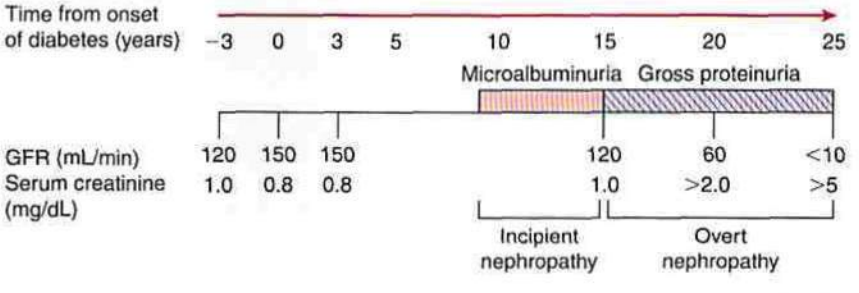


FIGURE 8-34. Time course of development of diabetic nephropathy. The relationship of time from onset of diabetes, the GFR, and the serum creatinine are shown. (Reproduced, with permission, from Kasper DL et al (eds). *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 2164, as modified from DeFronzo RA., *Therapy for Diabetes Mellitus and Related Disorders*. American Diabetes Assoc. Alexandria VA, 1998.)

- **Light microscopy**: Thickening of the GBM and expansion of the mesangium. Classic **Kimmelstiel-Wilson** lesions, areas of nodular glomerulosclerosis, may be found (see Figure 8-35).

Treatment

Treatment should be started for patients long before their symptoms have progressed to overt nephrotic syndrome.

- Patients who develop microalbuminuria should be started on **ACE inhibitors**, which have been shown to delay the progression of nephropathy in diabetic patients.
- **Good glucose control** with diet, exercise, and hypoglycemic agents has also been shown to delay the development and progression of symptoms.

Prognosis

Progression to nephrotic-range proteinuria in these patients is an example of severe progression of disease. ESRD typically develops within 5–10 years following these symptoms.

KEY FACT

Remember: Kimmelstiel-Wilson "wire loop" lesions in diabetic nephropathy.

Renal Amyloidosis

Results from the deposition of fibrous, insoluble proteins in the extracellular space of organs, in this case the glomerulus. Amyloidosis is a **multisystemic disorder of protein folding**, and can be acquired or hereditary. The two types that affect the kidneys are:

- **Amyloid L (AL)**, or immunoglobulin light chain, is associated with multiple myeloma.
- **Amyloid A (AA)**, associated with chronic inflammatory conditions such as RA.

Presentation

Nephrotic-range proteinuria is the clinical correlate to renal involvement by amyloidosis.

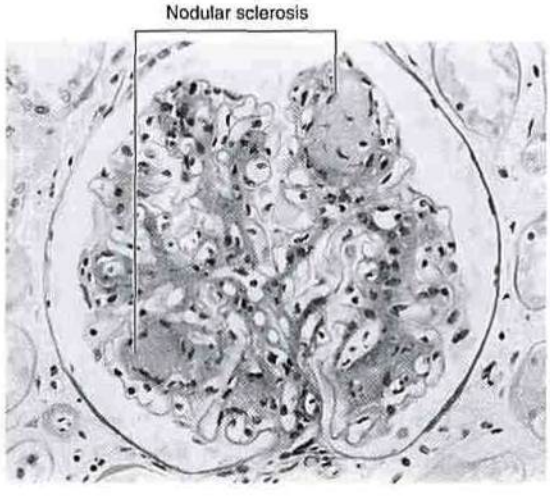


FIGURE 8-35. Diabetic nephropathy, showing nodular glomerulosclerosis (Kimmelstiel-Wilson disease). (Reproduced, with permission, from Chandrasoma P, Taylor CR, *Concise Pathology*, 3rd ed. Originally published by Appleton & Lange. Copyright © 1998 by The McGraw-Hill Companies, Inc.)

KEY FACT

Apple-green birefringence = amyloidosis.

Diagnosis

Definitive diagnosis is based on either renal, abdominal fat pad, or rectal biopsy.

- **Light microscope**: Tissue stained with **Congo red** has deposits of amyloid that show **apple-green birefringence** under polarized light. In addition, there is mesangial expansion with amorphous hyaline material (amyloid) and thickening of the GBM.

Treatment

Some improvement has been shown with a combination of **melphalan and prednisone.** Treatment for **AA** amyloidosis is based on the **underlying cause** of the condition. Transplantation is an option for patients with both AA and AL amyloidosis, although extrarenal organ involvement may prohibit this option.

Prognosis

Prognosis for renal involvement by **AL** is uniformly poor.

Lupus Nephritis

A part of the pathophysiologic spectrum of SLE.

Presentation

SLE patients may or may not have symptoms of kidney disease during its early course. However, as the disease progresses, kidneys are almost uniformly affected, and patients present with either nephrotic or nephritic syndrome, or both, ultimately leading to ESRD. Most common symptoms resulting from glomerular pathology include weight gain, high BP, and darker foamy urine, or swelling around the eyes, legs, ankles, or fingers.

Diagnosis

Suspect development of lupus nephritis once a patient is diagnosed with SLE. Gold standard to confirm renal involvement is renal biopsy. According the WHO there are five classes of renal involvement:

- **Class I**: No evidence of disease, normal histology.
- **Class II**: Mesangial involvement.
- **Class III**: Focal proliferative nephritis.
- **Class IV**: Diffuse proliferative nephritis.
- **Class V**: Membranous nephritis, characterized by extreme edema and protein loss.

Treatment

Depends on the level of renal involvement:

- **Class I**: General SLE treatment.
- **Class II**: Typically responds well to corticosteroids.
- **Class III**: Successfully responds to high doses of corticosteroids.
- **Class IV**: Mainly treated with corticosteroids and immunosuppressant drugs.
- **Class V**: Attend to the general symptoms.

Prognosis

Chiefly depends on age of onset, and the overall systemic involvement and response to therapy. Lupus nephritis (especially classes II, IV, and V) will ultimately lead to ESRD.

NEPHRITIC SYNDROME

The pathology of this condition is the result of **inflammation of the glomerulus.** Nephritic syndrome is characterized by a complex of symptoms consisting of:

- **Hematuria** secondary to destruction of glomerular capillaries and loss of RBCs into Bowman's space, resulting in dysmorphic RBCs and RBC casts on urinalysis.
- **Oliguria** secondary to the glomerular injury as a result of infiltration of inflammatory cells and immune complex deposition. This leads to obstruction of the glomerular capillary lumen, thus decreasing the GFR, ensuing both oliguria (<400 mL/day) and **azotemia** (increase of BUN and creatinine).
- **Hypertension** secondary to the increased fluid retention by the kidney due to the decreased GFR. Mild **proteinuria** may be observed as a result of the glomerular capillary injury.

KEY FACT

Hematuria, oliguria, azotemia, and hypertension are the hallmarks of nephritic syndrome.

As with nephrotic syndrome, there are **many different types** of nephrItic syndrome, each with a specific cause and presentation, yet all displaying the core nephritic symptoms mentioned above. The **presumptive diagnosis** is made through clinical suspicion, while the **definitive diagnosis** can only be made with renal biopsy. The **cause** of this condition is important, since as with nephrotic syndrome, it has implications for both treatment and prognosis.

KEY FACT

Proper diagnosis of different types of nephrItic syndrome requires **detailed history, serum chemistry, urinalysis, and pathology.**

Important **serologic markers** to obtain when nephritic syndrome is suspected include **C3 levels, anti-GBM titer,** and **antineutrophil cytoplasmic antibody (ANCA) titer.** The corresponding patterns of these laboratory findings may obviate the need for renal biopsy in some cases.

Acute Proliferative Glomerulonephritis (Poststreptoccocal/Infectious)

This form of nephritic syndrome most frequently develops following an infection with certain strains of **group A β-hemolytic streptococci** (GABHS). Pathogenesis is secondary to immune-complex deposition in the glomerulus with resulting complement activation and inflammation. Patients are typically children between the ages of 2 and 6 years due to the effective immunity one develops after infection.

Presentation

Classic presentation is **nephritic syndrome**, usually 10 days after pharyngeal infection or 2–3 weeks after skin infection with **group A β-hemolytic streptococci.** Patients tend to be children between the ages of 2 and 6, although adults occasionally develop this disease as well.

KEY FACT

Older children and young adults can also be affected with this form of nephritic syndrome.

Diagnosis

Effective diagnosis can be made based on history and clinical findings reflecting common nephritic symptoms.

- **Serum chemistry**: Antistreptolysin-O (ASO) titers, or other streptococcal antibodies (anti-DNAase B) are **elevated** in > 90% of patients. **C3** levels tend to be **low**; ANCA and anti-GBM antibodies are **negative.**
- **Urinalysis**: "Smoky brown" colored urine, RBCs and RBC casts, and in some instances proteins.
- **Pathology**: Renal biopsy if needed.
  - **Light microscopy** (see Figure 8-36): Hypercellular and enlarged glomeruli.



FIGURE 8-36. Light microscopy of acute proliferative glomerulonephritis. This low-power view shows three enlarged, hypercellular glomeruli (hypercellularity caused by proliferation of mesangial cells, endothelial cells, and global leukocytic infiltration in all lobules of the glomerulus). Several tubules contain red cells and proteinaceous material. Mild interstitial edema is also evident. (Courtesy of Uniformed Services University of the Health Sciences.)

KEY FACT

Keep an eye out for periorbital and/or facial edema.

- **Electron microscopy**: Characteristic subepithelial electron-dense deposits (**humps**).
- **Immunofluorescence**: IgG and C3 coarse granular deposits, with a "**lumpy–bumpy**" appearance.

Treatment

Conservative therapy aimed at maintaining proper water and electrolyte balance. **Diuretics** and other **antihypertensive** drugs are used to control the hypertension and edema that may develop. Penicillin can be considered in order to avoid contamination of contacts with a nephritogenic strain of streptococci, yet it is rarely administered.

Prognosis

Excellent in **children**, with complete recovery when adequately treated. In **adults** complete recovery can also be achieved, although the risk of developing RPGN is greater, as is progression to ESRD due to residual renal impairment.

Rapidly Progressive Glomerulonephritis (Crescentic RPGN)

RPGN is **not a disease**, per se, but rather is a malignant form of nephritic syndrome, in which progressive loss of kidney function occurs within weeks or months following the primary insult. The disorder is most common in adults aged 30–60 years, and is slightly more common in men.

Presentation

Classic nephritic syndrome; varies based on the underlying cause. There are **three distinctive types of RPGN**:

- **Type I**: Associated with Goodpasture's syndrome. **ANCA-negative**, with linear IgG and C3 deposits along the GBM.
- **Type II**: Associated with poststreptococcal GN, SLE, IgA nephropathy, and Henoch–Schönlein purpura. **ANCA-negative**, granular "lumpy-bumpy" deposits on immunofluorescence.
- **Type III–pauci-immune type**: Associated with Wegener's granulomatosis or idiopathic. There are no deposits on the GBM; however, it is **ANCA-positive**.

Diagnosis

Effective diagnosis can be made based on history and histologic findings.

- **Serum chemistry:**
  - BUN and creatinine may rise rapidly.
  - Anti-GBM-antibody-positive (in association with Goodpasture's syndrome).
  - ANCA presence varies based on the underlying cause.
  - Complement levels may be decreased in some cases.
- **Urinalysis:** Blood (RBCs), protein, WBC (monocytes), and casts.
- **Pathology:** Renal biopsy.
  - **Light microscopy** confirms crescent formation. Crescents largely consist of proliferated glomerular parietal cells; Bowman's space is filled with monocytes and macrophages. Large amounts of **fibrin** accumulate within the cellular layers of the crescents.

Treatment

Depends on the underlying cause. Refer to their underlying conditions.

Anti-Glomerular Basement Membrane Disease (Goodpasture's Syndrome)

Disease characterized by **antibodies against proteins in the GBM**. Symptoms can be isolated to the kidney or may also be seen in the lung due to cross-reactivity of antigens (**α-3 chain of collagen type IV**) that are common to both alveolar and GBMs. The underlying pathogenesis is based on a type II hypersensitivity reaction. This disease accounts for < 1% of glomerulopathies.

KEY FACT

Between 50% and 70% of cases present with both renal and pulmonary symptoms.

- **Goodpasture's syndrome:** Both alveolar and glomerular symptoms occur.
- **Idiopathic anti-GBM disease:** Symptoms are isolated to the kidney.

Presentation

Hematuria and other nephritic symptoms, subnephrotic range proteinuria, and rapidly progressive renal failure (RPGN) over the course of a few weeks is common. Pulmonary hemorrhage presenting with **hemoptysis** and dyspnea occurs in those patients with both glomerular and alveolar injury.

Diagnosis

Gold standard is renal biopsy with immunofluorescence. Chest X-ray will show bibasilar shadows in cases in whom pulmonary involvement has occurred.

- **Serum chemistry: Anti-GBM antibodies** are **positive** in > 90% of patients. ANCA levels are typically negative, but are occasionally mildly elevated. C3 levels are normal.
- **Urinalysis:** RBCs, RBC casts, and mild proteinuria.
- **Pathology:** Renal biopsy is the gold standard for proper diagnosis.
  - **Light microscopy:** Cellular accumulation in the Bowman's space; crescent formation.
  - **Immunofluorescence** (see Figure 8-37): **Linear, ribbon-like** (as opposed to granular in the immune complex etiologies detailed above) deposits of IgG along the GBM.

KEY FACT

Hemoptysis and hematuria = Goodpasture's syndrome or Wegener's granulomatosis.

Treatment

Emergency **plasmapheresis** is performed daily until anti-GBM titers become negative.

- **Prednisone** and either **cyclophosphamide** or **azathioprine** are started simultaneously to suppress formation of new GBM antibodies.
- Patients are monitored frequently for rising titers of anti-GBM antibodies, and receive plasmapheresis as needed.

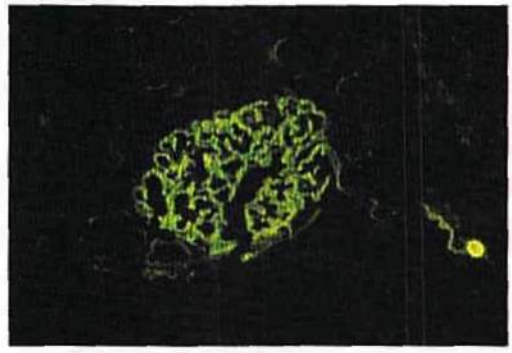


FIGURE 8-37. Anti-glomerular basement membrane (IgG) in Goodpasture's syndrome. Note the continuous, linear staining for IgG (anti-GBM antibodies) along the glomerular capillary loops—a classic finding in Goodpasture's. (Courtesy of PEIR Digital Library [http://peir.net].)

Prognosis

Without treatment, patients tend to develop ESRD within 1 year. With immunosuppressive regimines, > 90% of patients maintain renal function after 1 year if aggressive therapy is started early. Although this disease is rare, the diagnosis must be made **early** to ensure adequate treatment and good prognosis.

KEY FACT

The association of this disease with a recent mucosal infection suggests an exaggerated IgA response.

IgA Nephropathy (Berger's Disease)

IgA nephropathy is a condition that usually affects **children and young adults**. It is suspected to arise in individuals with an abnormality in IgA production and clearance (increased production of IgA in ~ 50% of individuals with this disease), leading to deposition of the antibodies in the mesangial matrix, which leads to glomerular injury and nephritic symptoms. It is the **most common** glomerulopathy worldwide.

IgA nephropathy can present as disease limited to the kidneys, or as a component of **Henoch-Schönlein purpura** (see Figure 8-38).

KEY FACT

Painless hematuria following infection, think Berger's disease.

Presentation

Episode of gross hematuria 24–48 hours after a nonspecific upper respiratory tract infection or GI infection. **Hematuria** typically lasts for several days and then spontaneously resolves, only to recur every few months. Hypertension is unusual at presentation.

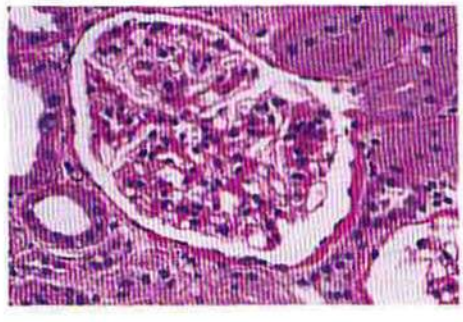


FIGURE 8-38. Light microscopy of IgA nephropathy. IgA nephropathy can have variable histologic findings, ranging from normal to overt crescentic GN. The glomerulus in this high-power view (periodic acid-Schiff [PAS] stain) shows mild changes consisting of segmental proliferation of mesangial cells and mesangial widening by matrix accentuated by the PAS stain. (Courtesy of Uniformed Services University of the Health Sciences.)

Diagnosis

Suspected in patients with new-onset hematuria within 1–2 days of either an upper respiratory or GI infection.

- **Serum chemistry**: ANCA- and anti-GBM-**negative**, C3 levels are **normal**.
- **Urinalysis**: Painless spontaneous hematuria.
- **Pathology**: Renal biopsy.
  - **Light microscopy** (see Figure 8-38): May range from normal to overt crescentic.
  - **Immunofluorescence** (see Figure 8-39): IgA deposits with specific distribution in mesangial cells.

Treatment

There is no proven therapy for this disorder.

Prognosis

Most patients have recurring episodes every few months or during mucosal infections. Between 20% and 50% of patients suffer ESRD after 20 years.

Hereditary Nephritis (Alport's Syndrome)

Alport's syndrome is a **hereditary form of glomerular injury** that is typically **X-linked**, caused by an error in the synthesis of the **α-5 chain of type IV collagen**. This form of collagen is a major component of the GBM, and defects lead to renal dysfunction. Type IV collagen is also found in many other tissues, and therefore patients with this genetic defect tend to develop **nerve deafness, lens dislocation**, and early development of **cataracts**.

Presentation

Patients are typically between 5 and 20 years old. Initially, Alport's syndrome is asymptomatic. Later stages are characterized by chronic glomerulonephritis and systematic glomerular destruction, leading to hematuria and affecting the GFR, ultimately leading to ESRD.

Diagnosis

Based on the following findings:

- **Serum chemistry**: ANCA- and anti-GBM-**negative**, C3 levels are normal.
- **Urinalysis**: Gross hematuria, mild proteinuria.

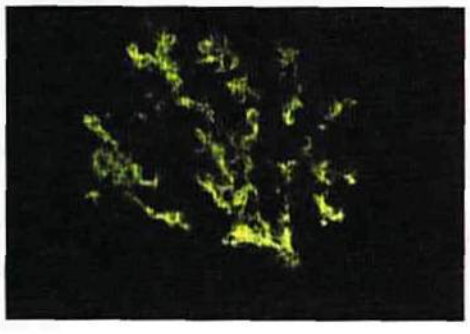


FIGURE 8-39. Immunofluorescence of IgA nephropathy. Immunofluorescent stain shows deposits of IgA primarily in mesangial regions. (Courtesy of Uniformed Services University of the Health Sciences.)

CLINICAL CORRELATION

IgA nephropathy associated with extrarenal symptoms is referred to as **Henoch-Schönlein purpura.**

FLASH BACK

Henoch-Schönlein purpura's extrarenal symptoms include:

- Skin: Purpural lesions found on the extensor surfaces of the lower extremities and buttocks, and arms.
- GI symptoms: Abdominal pain, intestinal bleeding.
- Musculoskeletal: Joint pain.

KEY FACT

Male patients exhibit full spectrum of this disease: Deafness, cataracts, and renal failure.

Female patients are carriers; symptoms are limited to mild hematuria.

KEY FACT

Confirmation of renal involvement is necessary to make a definitive diagnosis of Wegener's granulomatosis.

FLASH BACK

Chronic sinusitis, hemoptysis, and hematuria—think Wegener's granulomatosis.

CLINICAL CORRELATION

Respiratory involvement presents as paranasal sinus pain, drainage of bloody nasal discharge, hemoptysis, dyspnea, or chest discomfort. **Dermatologic, cardiac,** and **nervous system** involvement can also be seen.

CLINICAL CORRELATION

Alkalinize the urine in clinical conditions that may trigger uric acid stone formation.
Most commonly used agents are **carbonic anhydrase inhibitors (acetazolamide).**

- Pathology: Renal biopsy.
  - **Light microscopy:** Glomerular and mesangial proliferation. **Foam cells** may be present, which are interstitial cells with accumulation of lipids.
  - EM: Splitting of the lamina densa (component of GBM).

Treatment

No specific therapy. Dialysis is used for patients that progress to ESRD. Renal transplantation is an option for those patients in renal failure, as allografts do not have similar genetic mutations. Because Alport's syndrome is X-linked, this disorder is more severe in **males** than in females.

Wegener's Granulomatosis

Wegener's granulomatosis is a systemic disease that presents as focal necrotizing vasculitis and necrotizing granulomas in the lungs (involvement of both upper and lower respiratory tract), in association with necrotizing glomerulonephritis. Renal injury occurs in up to 80% of patients with this disorder.

Presentation

Patients typically present with **non-specific symptoms**, such as fever, arthralgias, lethargy, and malaise. Renal involvement presents with **nephritic** symptoms and an occasional **mild proteinuria**.

Diagnosis

ANCA-positive in 80% of patients with renal involvement.

- Biopsy is required, and demonstrates focal, segmental necrotizing glomerulonephritis with occasional crescent formation. Unlike in respiratory tract tissue biopsies, granulomas are only rarely seen. There is a lack of immunoglobulin or complement on immunofluorescence, **anti-GBM** is **negative**, and **complement levels** are **normal**.

Treatment

Glucocorticoids and cyclophosphamide. Dialysis and renal transplantation are good options for those patients that progress to ESRD with little recurrence of the disorder in the allograft.

RENAL STONES (UROLITHIASIS)

Stone formation can take place anywhere in the urinary collecting system (most commonly in the kidneys) and largely depends on sex, age, diet, climate, and genetic makeup. Their size can vary from crystals to large stones. They are more common in men and tend to recur. There are several different types:

- **Calcium oxalate/phosphate stones** are the most common; followed by struvite, uric acid, and cystine stones (see Table 8-16). They occur when patients absorb more calcium in the gut than they excrete in the urine, or have a primary renal defect of calcium reabsorption. Fewer patients have hypercalcemia secondary to hyperparathyroidism, vitamin D intoxication, or sarcoidosis.
- **Struvite (magnesium ammonium phosphate) stones** occur in patients with persistently alkaline urine from UTIs caused by **urease-positive** organisms, such as *Proteus vulgaris* or staphylococci. When the stone creates a cast of the renal pelvis and calyceal system, it is referred to as a **staghorn kidney stone.**

TABLE 8-16. Common Types of Kidney Stones

Stone Type	Frequency	Causes	Radiology
Calcium oxalate and calcium phosphate	**Most common**	▪ Hypercalcemia: cancer, ↑ PTH, ↑ vitamin D, milk-alkali syndrome, **idiopathic.**	**Radiopaque.**
Struvite (ammonium magnesium phosphate)	Second most common	▪ UTI with urease-positive bacteria (*P. vulgaris* or *Staphylococcus*).	Radiopaque; stone creates a cast of the renal pelvis and calyceal system.
Uric acid	Less common	▪ Hyperurecemia: gout. ▪ High cell turnover: leukemia and myeloproliferative diseases.	Radiolucent.
Cystine	Less common	▪ Cystinuria: genetic conditions deficient in cystine, ornithine, lysine, and arginine.	Radiolucent.

- **Uric acid stones** are associated with **gout** or diseases that cause rapid cell turnover (**leukemia**, myeloproliferative diseases). They are more likely to form in **acidic urine**.
- **Cystine stones** are seen in patients with genetic defects in the metabolism of cystine, ornithine, lysine, or arginine. They are more likely to form in **acidic urine**.

Presentation

Kidney stones classically present with severe flank pain that **radiates to the groin** and is colicky in nature. **Hydronephrosis** and **infection** proximal to the site of obstruction can occur as a result of prolonged impediment of the urine outflow.

FLASH BACK

Tumor lysis syndrome can result in formation of uric acid crystals and stones. **Avoid ARF** by alkalinization of urine, allopurinol, and proper hydration.

Diagnosis

- **Abdominal X-rays** (see Figure 8-40) are of benefit in cases of calcium oxalate, calcium phosphate, and struvite stones (which are **radiopaque**), but of no value in uric acid and cystine stones, which are **radiolucent** and cannot be visualized on a radiograph. Thus, non-contrast CT is valuable in diagnosing such cases.
- **Urinalysis** will likely show hematuria.

Treatment

Mainly depends on the size of stones. **Increased fluid intake** and appropriate **pain management** while waiting for the stone to pass is sufficient for stones < 9 mm. Larger stones, however, require either a noninvasive approach, such as extracorporeal shockwave **lithotripsy** (ESWL) or surgical treatment (**nephrolithotomy**).



FIGURE 8-40. Calculi (kidney stones). Note three separate deposits of calcified density confined to the right renal shadow. The largest one measures 2 cm in greatest diameter. (Reproduced, with permission, from Chen MYM, Pope TL Jr., Ott DJ, *Basic Radiology*, New York: McGraw-Hill, 2004: 204.)

URINARY TRACT INFECTIONS

UTIs are infections, usually bacterial, of the **lower urinary tract**. They are extremely common in several different populations and settings:

- **Outpatient:** Especially common among young sexually active females, and are thought to be due to the short female urethra and the small distance between the urethra and the anus.
- **Inpatient:** Very common, especially with Foley catheter use. Likely to be asymptomatic. Have a high suspicion for UTI in any febrile inpatient.
- **Pregnancy:** Asymptomatic bacteriuria is common in pregnant women. There is a higher risk for UTIs to develop into pyelonephritis in pregnant women. UTIs also raise the risk for preterm labor and low birth weight. Bacteriuria in a pregnant woman should **always** be treated, whether or not it is symptomatic.
- **Children:** Children with recurrent UTIs should be evaluated for vesicoureteral reflux (VUR).

Presentation

- Dysuria, frequency, urgency, suprapubic pain, and hematuria.
- In an uncomplicated UTI, there should **NOT** be fever, nausea, vomiting, or costovertebral angle (CVA) tenderness.

Diagnosis

Can be made by history alone.

- Clean-catch UA will usually show pyuria (PMNs in the urine), bacteriuria, leukocyte esterase, and nitrites.
- Urine culture will identify the specific pathogen but is only indicated for inpatients, for patients who have failed antibiotic therapy, or for other complicated cases of UTI.

Treatment

Antibiotic therapy appropriate for the causative micro-organisms.

Acute Pyelonephritis

Pyelonephritis is an infection, usually bacterial, of the upper urinary tract including the kidneys. It typically results from an ascending infection from the lower urinary tract. It affects the same populations as uncomplicated UTIs but in much smaller numbers overall.

Presentation

Fever, nausea/vomiting, flank pain and CVA tenderness. Can occur in the presence **or** absence of typical symptoms of lower UTI (dysuria, frequency, urgency).

CLINICAL CORRELATION

White cell casts in the urine are pathognomonic for acute pyelonephritis.

Diagnosis

Based on **history** and **physical** exam, especially vital signs and CVA tenderness.

- UA and **urine culture** with **antimicrobial sensitivities** should be performed in all patients with suspected acute pyelonephritis because of the risk of negative sequelae if treatment is inappropriate. Urinalysis will demonstrate **pyuria. White cell casts**, if present, are diagnostic of acute pyelonephritis.
- **Microbiology:** The pathogens responsible for pyelonephritis are the same as those responsible for uncomplicated UTIs.

Treatment

Antibiotic therapy appropriate for the causative micro-organisms.

Chronic Pyelonephritis

Recurrent or persistent infections of the kidneys ultimately lead to irreversible pathologic changes in the corticomedullary region of the kidneys.

- **Underlying factors** leading to this condition are almost exclusively structural abnormalities such as **obstructions** of the urinary tract (i.e., from stones or BPH) or in **children** with vesicoureteral reflux **(VUR).**

Presentation

- May have asymptomatic pyuria.
- May complain of low-grade fevers, flank pain, and nausea/vomiting.
- May have evidence of renal insufficiency such as hypertension, proteinuria, or failure to thrive in children.

Diagnosis

Based on the following findings:

- **Renal ultrasound** to evaluate for renal damage. A **CT scan** may offer additional information for diagnosing the underlying pathology.
- **Voiding cystourethrogram** can help diagnose VUR in children.
- Laboratory data may show **pyuria, proteinuria**, and **azotemia**.
- **Pathologic specimens:**
  - Chronic inflammation and asymmetric corticomedullary scarring.
  - Deformities in renal pelvis and calyces.
  - **Thyroidization** of kidney.

Treatment

Depends on the underlying cause; antibiotics and surgical repair.

DIFFUSE CORTICAL NECROSIS

CLINICAL CORRELATION

Associated with diffuse cortical necrosis:

- Abruptio placentae
- Eclampsia
- Septic shock
- Hemolytic uremic syndrome (in children)

Diffuse cortical necrosis (DCN) develops as a result of diffuse or patchy **infarction of the cortices** (cortical necrosis) of the kidney secondary to ischemia. Often multi-factorial, and can progress to ARF, especially in the third trimester of pregnancy.

Presentation

Signs and symptoms of the systemic process (sepsis, DIC, obstetric complications) resulting in cortical necrosis; polyuria and evidence of ARF.

Diagnosis

Based on the following findings:

- **Serum chemistry:** Azotemia, DIC (low platelets, increased fibrin split products).
- **Urinalysis:** Proteinuria, hematuria, red cell casts, granular casts.
- **Pathology:** Cortical necrosis, microthrombi of small vessels.

Treatment

Treat underlying condition.

Prognosis

Reversible if treatment of underlying process is initiated early.

RENAL PAPILLARY NECROSIS

CLINICAL CORRELATION

Associated with renal papillary necrosis:

- DM
- Acute pyelonephritis
- Chronic phenacetin use

Renal papillary necrosis results from an ischemic insult to the renal papillae.

Presentation

Polyuria, rust-colored urine, ARF, flank pain.

Diagnosis

UA: Sediment, casts, blood, and necrotic renal papillae. Plain radiographs may show a ring of calcification (**nephrocalcinosis**), especially in disease resulting from analgesic use.

Treatment

Treat underlying disease.

RENAL FAILURE

Many conditions can lead to either ARF or CRF (CKD). Typical pathophysiologic mechanisms and pathologies are addressed in this section.

Acute Renal Failure

Abrupt-onset decrease in renal function as measured by GFR, not necessarily urine output. Leads to reduced ability to maintain serum electrolytes and excrete nitrogenous waste. ARF is classified as shown in Figure 8-41.

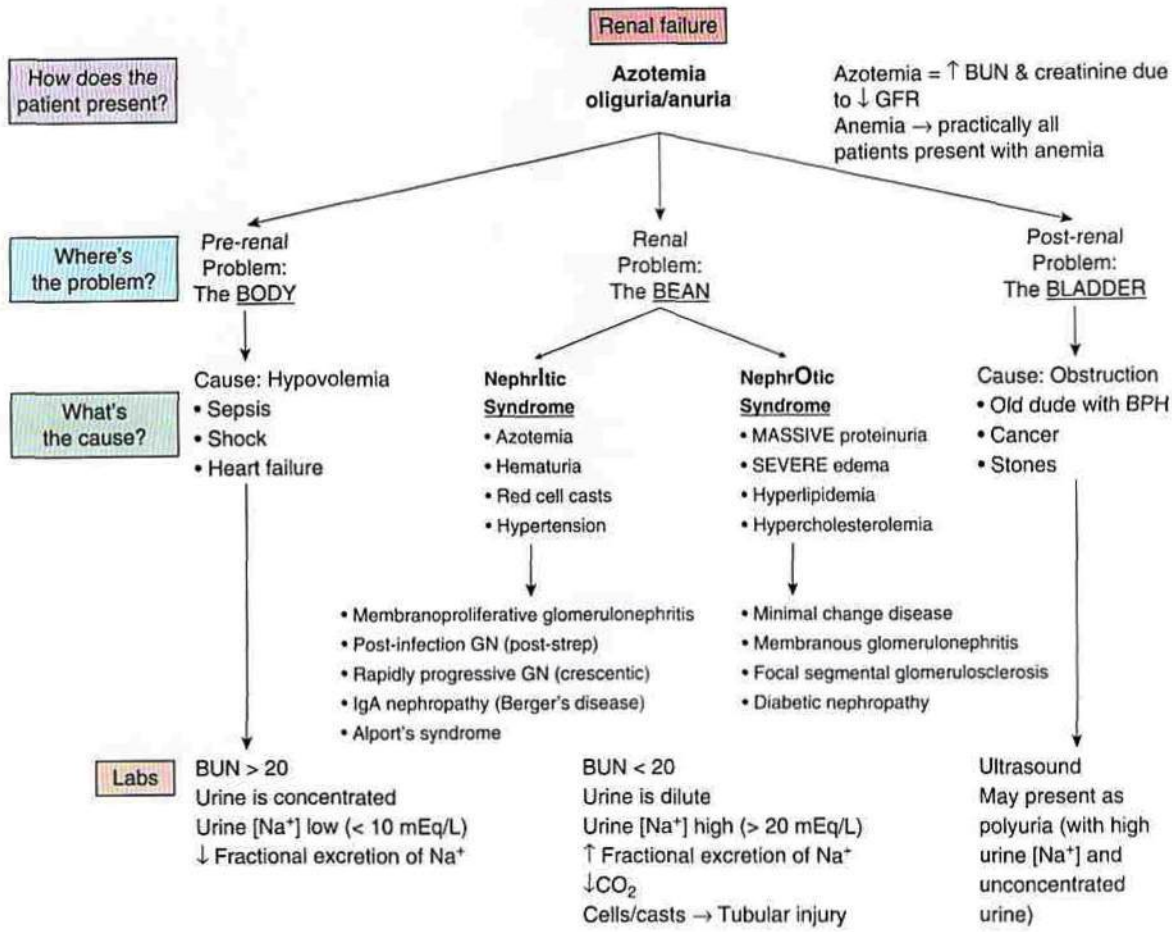


FIGURE 8-41. Pathophysiology of renal failure.

TREATMENT

- Maintain fluid and electrolyte balance and avoid nephrotoxic medications.
- Treat obstruction as indicated.
- **Dialysis** is indicated for severe uremia, hyperkalemia unresponsive to medication, metabolic acidosis, refractory fluid overload (usually presents as pulmonary edema), pericarditis, etc.

Acute Tubular Necrosis

A disease state of the kidney clinically manifested as ARF, and pathologically by destruction of tubular epithelial cells. Acute tubular necrosis (ATN) is an intrinsic renal disease and is the **most common cause of ARF**. It can be either ischemic or nephrotoxic in origin (see Table 8-17).

CLINICAL CORRELATION

Associated with ATN:
- Muddy brown casts
- Rhabdomyolysis
- Crush injury

TABLE 8-17. Common Causes of ATN

TYPE	ETIOLOGY
Nephrotoxic	▪ **Drugs:** NSAIDs, radiocontrast, cyclophosphamide, aminoglycosides, and diuretics. ▪ **Disease:** rhabdomyolysis, hemolysis, gout, pseudogout, and multiple myeloma.
Ischemic	▪ Decreased blood flow to the kidney.

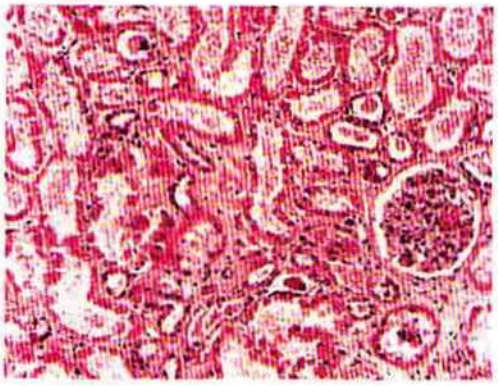


FIGURE 8-42. Kidney with ATN (loss of nuclei), dilation of tubules, interstitial edema, sloughing of epithelium, and glomerular congestion. (Courtesy of Uniformed Services University of the Health Sciences.)

Presentation

Often asymptomatic; may have oliguria and azotemia. If left untreated, signs and symptoms of uremia and fluid overload develop.

Diagnosis

Azotemia; urinalysis: FeNa > 1% and **muddy brown casts** on microscopy (see Figure 8-42).

Treatment

Address the underlying disease and remove the offending agent (medication, contrast, etc.). When rhabdomyolysis or crush injury is the insulting factor, large volumes of IV fluid are required to maintain adequate perfusion. Look for and treat electrolyte abnormalities.

Chronic Renal Failure

Also called CKD, characterized by a substantial decrease in renal function, usually less than 20% of normal GFR, occurring over a long period of time (usually > 6 months). CKD can be asymptomatic for many years, with increasing uremia and associated symptoms as GFR drops below 60 mL/min. Causes of CRF, all of which are chronic long-term disease processes, are shown in Table 8-18.

TABLE 8-18. Causes of CRF

	Cause
Prerenal	▪ Renal artery stenosis ▪ Embolism (both kidneys)
Parenchymal	▪ DM ▪ SLE ▪ Hypertension ▪ Amyloidosis ▪ Chronic glomerulonephritis ▪ Chronic tubulointerstitial nephritis ▪ Adult polycystic kidney disease ▪ Renal cancer
Postrenal	▪ Chronic urinary tract obstruction

TREATMENT

- Dietary management of protein and electrolytes.
- Dialysis (indicated when GFR ≤ 20 mL/min).
- Renal transplantation (cadaveric or living donor) when GFR < 20 mL/min.

Renal Failure: Key Definitions

Glomerular filtration rate (GFR): The volume of filtrate that crosses the glomerular capillary membrane into Bowman's capsule per unit time. Normal is 115–125 mL/min.
Azotemia: Elevated BUN and serum creatinine levels; may have causes other than renal dysfunction.
Uremia: Syndrome of biochemical derangement characterized by azotemia, acidosis, hyperkalemia, poor control of fluid volume, hypocalcemia, anemia, and hypertension.
Oliguria: Urine output < 500 mL/24 hours.
Anuria: Urine output < 100 mL/24 hours.
Polyuria: Urine output > 3 L/24 hours.

Consequences of Renal Failure

Renal failure results in multiple systemic consequences (see Table 8-19). The primary effects of ARF are electrolyte imbalances and disruption of the kid-

TABLE 8-19. Consequences of Renal Failure

Uremic syndrome	▪ Occurs as BUN rises; lethargy, seizures, myoclonus, asterixis, pericardial friction rub. ▪ Urea typically travels from the liver to the kidney where it is excreted. The failing kidney cannot excrete urea and therefore the gut enzyme urease converts the extra urea into ammonia, causing **hyperammonemia.** ▪ Urinalysis: **Isosthenuria (specific gravity of urine becomes fixed around 1.010, regardless of the fluid intake),** proteinuria, abnormal sediment with tubular casts.
Hyperkalemia	▪ When GFR significantly decreases the kidney cannot excrete dietary K^+. ▪ Hyperkalemia → look for **peaked T waves on ECG which can lead to ventricular fibrillation.**
Metabolic acidosis	▪ GFR < 50% impairs renal production of HCO_3 so H^+ cannot be excreted. This causes an **AG acidosis.**
Sodium and water retention	▪ **Early CRF** causes **decreased urine concentration** which causes easy dehydration and Na wasting. ▪ **Late CRF** causes **volume overload** as the kidney is no longer able to excrete Na. This can lead to **CHF** and **pulmonary edema.**
Renal osteodystrophy	▪ Vitamin D is converted by 1-α hydroxylase in the liver to the active form 1,25-$(OH)_2$ vitamin D which increases absorption of dietary and bone Ca^{2+} and PO_4. ▪ CRF causes loss of 1-α hydroxylase activity in the kidney, thereby causing decreased vitamin D activation and increased bone turnover.
Anemia	▪ Failure of **EPO production** causes decreased hematocrit.
Hypertension	▪ **Benign hypertension** causes hyaline arteriolosclerosis. Malignant hypertension and malignant nephrosclerosis occurs when there is fibrinoid necrosis of the arterioles, small arteries, and intravascular thrombosis. ▪ Long-standing damage and scaring of the kidney from reflux nephropathy will cause hypertension as one of the first indications of renal disease. ▪ Seen as a result of adult polycystic kidney disease (APKD).
Fanconi's syndrome	▪ Causes damage to proximal tubular reabsorption of glucose, amino acids, phosphate, and bicarbonate.

FLASH BACK

Expired tetracyclines can cause Fanconi's syndrome.

neys' control of excretion. ARF typically manifests itself as uremic syndrome, hyperkalemia, and metabolic acidosis. CRF has more gradual effects on multiple systems, and the deregulation of sodium and water can lead to **CHF and pulmonary edema.**

TUMORS OF THE RENAL SYSTEM

As with the other neoplasms, tumors of the renal system can be malignant or benign, as well as being primary and secondary (metastatic). In this section, we are addressing the most common malignancies of the kidneys.

Renal Cell Carcinoma

Renal cell carcinoma is the most common primary tumor of the kidney in the adult population, accounting for ~ 80% of kidney tumors (affecting men more than women, at an average age of 60–70 years). It arises from the tubular epithelium. An increased risk has been noted in smokers, with **cadmium exposure**, and with acquired cystic disease from chronic dialysis. Three common forms exist.

- **Clear cell carcinomas (= 80%)** have **clear or granular cytoplasm** (see Figure 8-43). Both familial and sporadic forms are commonly associated with an underlying genetic defect in the ***VHL* gene** (a tumor suppressor gene on **chromosome 3**).
- **Papillary renal cell carcinomas (= 15%)** have a **papillary growth pattern** and affect the proximal tubules. Familial and sporadic forms exist with the underlying genetic defect being in the ***MET* gene** (a proto-oncogene on chromosome 7). Familial forms frequently exhibit **trisomy of chromosome 7**.
- **Chromophobe renal carcinomas (< 5%)** affect the cortical collecting ducts, stain darkly, and are characterized by **loss of an entire chromosome.**

CLINICAL CORRELATION

Renal cell carcinoma can be associated with **von Hippel–Lindau disease.**

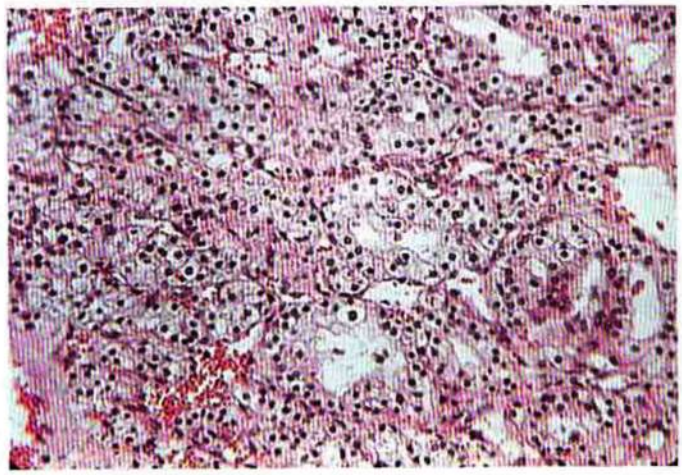


FIGURE 8-43. Clear cell carcinoma. Histologically, the clear cell variant is the most common type. The tumor has an alveolar architecture created by a prominent network of thin-walled vascular septae demarcating collections of tumor cells. Tumor cells have abundant clear cytoplasm. The nuclei are round and fairly uniform in appearance in low-grade tumors (as seen here), or may be highly pleomorphic and vesicular with prominent nucleoli in high-grade tumors. (Courtesy of PEIR Digital Library [http://peir.net].)

Presentation

A flank mass may be palpable, but the classic **triad of clinical symptoms** includes:

- Painless hematuria (microscopic or macroscopic).
- Fever.
- Flank pain.

The cancer may spread hematogenously via the IVC to the bones or lungs causing **bone** pain or a **lung** mass.

CLINICAL CORRELATION

Paraneoplastic symptoms:

- Hypercalcemia due to PTH-related protein.
- Polycythemia from excess EPO production.

Diagnosis

Ultrasound examination of the kidneys will show the presence of a mass, while **CT** offers additional information. **Chest X-ray** is important to look for metastatic disease.

Treatment

Standard treatment involves **radical nephrectomy** with removal of local lymph nodes.

- Partial nephrectomy/nephron-sparing surgery is commonly performed in cases of VHL.
- Additional treatments have included **interleukin-2** in metastatic disease.

Prognosis

The overall prognosis of renal cell carcinoma is poor, with the worst prognosis in metastatic disease and the best prognosis with the chromphobe subtype.

Transitional Cell Carcinomas

Transitional cell carcinomas are twice as common as renal cell carcinomas and affect men more than women, frequently between the ages of 50 and 70 years. They arise in the urinary tract outside of the kidney, predominantly in the bladder, originating from transitional epithelium.

- Bladder tumors are more common in people with exposures to **β-naphthylamine**, cigarette smoking, **cyclophosphamide**, and **schistosomiasis**.

MNEMONIC

Associated with problems in your Pee SAC.

Phenacetin
Smoking
Aniline dyes
Cyclophosphamide

Presentation

Painless hematuria with the risk factors mentioned and in the appropriate age range. Other presentations depend on the location of the tumor. If a ureter is involved or outflow of the ureters is blocked, there may be an obstructive presentation with flank pain, suprapubic fullness and pain, increased **urinary frequency**, and **hydronephrosis**.

Diagnosis

Cystoscopy will reveal the lesion within the bladder while **urine cytology** shows malignant cells. **Pelvic CT** may help with level of invasion.

Treatment

Superficial tumors may be treated with transurethral resection and/or injection of chemotherapeutic agents, such as **bacille Calmette–Guérin (BCG)**, into the bladder. More invasive tumors may require cystectomy with radiation and/or chemotherapy.

KEY FACT

Wilms' tumor is associated with loss of *WT1* on chromosome 11.

CLINICAL CORRELATION

Associated syndromes include:

- **WAGR** complex: **W**ilms' tumor, **A**niridia, **G**enitourinary malformation, and mental-motor **R**etardation.
- **Denys-Drash syndrome:** Gondal dysgenesis and renal abnormalities.
- **Beckwith-Wiedemann syndrome:** Organomegaly or hemihypertrophy.

Prognosis

Tend to recur following treatment.

Wilms' Tumor (Nephroblastoma)

Wilms' tumor is the **most common** primary tumor of the kidney in **early childhood (between 2 and 5 years)**, and is due to **loss of *WT1*** (a tumor suppressor gene on chromosome 11). **Nephrogenic rests**, or precursor lesions, are associated with bilateral Wilms' tumors.

Presentation

Large, palpable abdominal mass that may extend into the pelvis. Hemihypertrophy may be present. Tumors this size can also cause intestinal obstruction. Other presenting symptoms include abdominal pain, fever, and hematuria.

Diagnosis

Abdominal ultrasound will show an intrarenal mass and any invasion into the IVC. **CT** scan (chest, abdomen, and pelvis) can evaluate for metastatic disease.

- Grossly, these tumors are **tan-gray with areas of hemorrhage and necrosis.**
- Histologically, there is a variable mix of blastemal, stromal, and epithelial cell types.

Treatment

Nephrectomy with chemotherapy (vincristine, actinomycin D, and doxorubicin if lung metastases are found). Abdominal radiation may also be used in selected patients.

Prognosis

The above-mentioned therapy offers excellent 5-year survival rates.

ELECTROLYTE ABNORMALITIES

Electrolyte abnormalities can be diagnosed with standard chemistry panel **laboratory results** and are frequently the manifestation of some underlying pathology. The common electrolyte abnormalities are given below along with their definitions, presentations, causes, and treatments.

Hypernatremia

Serum sodium level > 145 mEq/L.

CLINICAL CORRELATION

Neurologic symptoms: irritability, delirium, coma, and doughy skin.

Presentation

Excessive thirst, doughy skin, and mental status changes (confusion, seizures, and muscle twitching).

Causes

Most commonly, hypernatremia is due to a loss of free water versus gain of sodium without adequate rehydration (due to impairment of the thirst mechanism or lack of access to water).

- Specific causes include iatrogenic from hypertonic saline, medications (diuretics, lithium, or sodium-containing drugs), hyperglycemia in the setting of diabetic ketoacidosis, and central or nephrogenic DI.

Treatment

Treatment includes correction of the underlying cause and IV hydration with normal saline or lactated Ringer's solution. The amount of IV fluid to give is determined by the following formula:

$$\text{Free water deficit} = \text{Total body water} \times [(\text{Plasma Na}/140) - 1]$$

Prognosis

Patients who becomes acutely hypernatremic have a worse prognosis than those in a chronic hypernatremic state, though both have a high associated mortality.

Hyponatremia

Serum sodium level < 136 mEq/L.

Presentation

The symptoms are largely manifested neurologically: Headaches, nausea, muscle cramps, depressed reflexes, and disorientation.

Causes

To identify the cause of hyponatremia, it is essential to identify **serum osmolality**. Table 8-20 offers an approach to identifying the cause of hyponatremia. Patients with low serum sodium and low serum osmolality are most frequently encountered (and most frequently tested).

Treatment

Treatment of hyponatremia depends on the underlying cause, but if the patient is symptomatic the administration of IV hypertonic saline (3% saline) may be indicated. Care must be taken to slowly correct the sodium level because of the risk that **central pontine myelinolysis** (CPM) may develop.

TABLE 8-20. Common Causes of Hyponatremia

1. Serum sodium < 136 mEq/L		
2. Determine serum osmolality		
High (> 285 mOsm)	**Low** (< 280 mOsm)	**Normal** (280–285 mOsm)
Hyperglycemia.		Hyperlipidemia Hyperproteinemia
3. Clinically determine the patient's volume status		
Hypovolemic	**Euvolemic**	**Hypervolemic**
Dry mucous membranes, poor skin turgor, rapid heart rate.	No signs of hyper- or hypovolemia.	Edema
GI losses, skin losses.	SIADH, water intoxication.	Liver failure, heart failure

CLINICAL CORRELATION

CPM is a neurologic disorder that develops as a result of severe damage to the myelin sheath of nerve cells in the pons.
Symptoms include: Sudden para- or quadriparesis, dysphagia, dysarthria, double vision, and loss of consciousness.

Hyperkalemia

Serum potassium > 5.0 mEq/L.

Presentation

Clinically, the patient may experience palpitations or muscle weakness. Potassium causes the heart to be more excitable (possibly leading to **ventricular fibrillation**) and the effects on the heart should be investigated with an **ECG** (see Figure 8-44):

- Peaked T waves
- Widening of the QRS complex
- Flattening of the P wave

KEY FACT

Lab error due to hemolysis of red cells in the preparation of the specimen may provide false-positive results for hyperkalemia.

Causes

Most common underlying pathology includes renal failure or trauma due to extensive crush injury with release of potassium from muscle cells.

Treatment

Treatment focuses on removing potassium from the body and stabilizing the myocardium (monitor the serum potassium levels and ECG findings during treatment). The systematic approach to hyperkalemia includes:

- **Calcium gluconate** is given first to stabilize the myocardium.
- Insulin with concurrent glucose infusion.
- β-Agonists (drive potassium into cells).
- Sodium polystyrene sulfonate (causes **excretion of potassium** from the GI tract).
- Dialysis.

Hypokalemia

Serum potassium < 3.6 mEq/L.

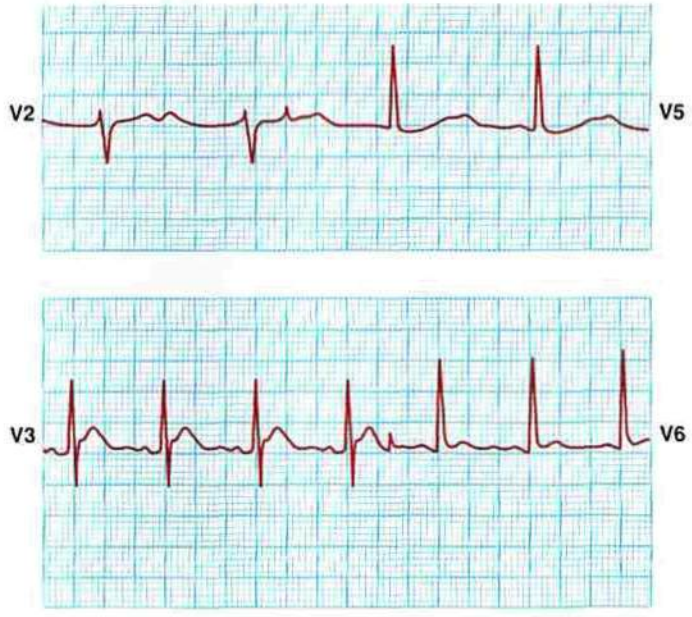


FIGURE 8-44. Electrocardiographic manifestations of hyperkalemia (upper strip) and hypercalcemia (lower strip).

Presentation

Patients will present with general, non-specific symptoms of fatigue, muscle weakness, intestinal ileus, and/or hyporeflexia.

Classic ECG findings (see Figure 8-45) include:

- Flattened T waves.
- Presence of U waves.
- ST-segment depression.

Causes

Insulin, alkalosis, diuretics (loop or thiazide), vomiting (think eating disorders), increased aldosterone levels, hypomagnesemia.

Treatment

Treat the underlying cause. Low-serum potassium is treated with administration of IV or PO potassium. During treatment, monitor the ECG and plasma levels.

Hypercalcemia

Serum calcium level > 10.2 mg/dL.

Presentation

Many patients will be asymptomatic. Levels over 12.0 mg/dL may produce ECG changes (**prolonged QT interval**; see Figure 8-46), and more dramatic symptoms, such as renal **stones** (nephrolithiasis), abdominal **moans** (nausea, vomiting, constipation), psychiatric **overtones** (delirium, psychosis), and painful **bones** (osteitis fibrosa cystica).

CLINICAL CORRELATION

Renal stones, abdominal moans, painful bones, and psychiatric overtones are classic findings for hypercalcemia.

Causes

The most common cause in the inpatient setting is **malignancy** (metastases to bone or exogenous production of PTH-related protein), while the most common cause in the outpatient is primary **hyperparathyroidism** (adenoma > hyperplasia > carcinoma). Other common causes include hyperthyroidism, thiazide diuretic use, granulomatous disease (sarcoidosis), renal failure, and **milk-alkali syndrome**.

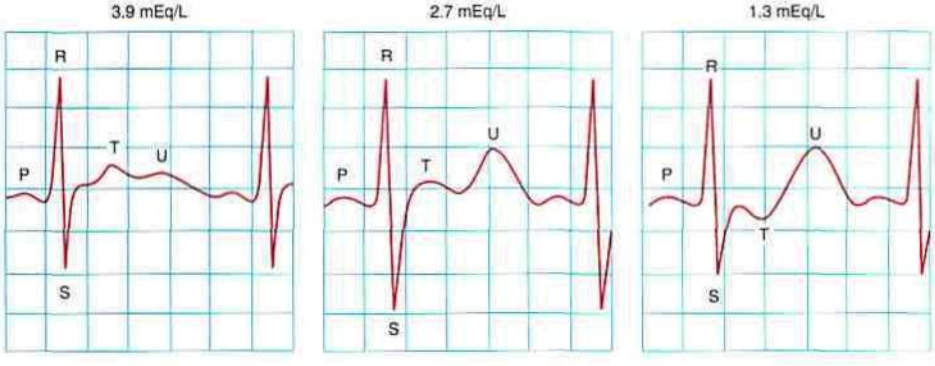


FIGURE 8-45. Electrocardiographic effects of hypokalemia. Note progressive flattening of the T wave, an increasingly prominent U wave, increased amplitude of the P wave, prolongation of the PR interval, and ST-segment depression. (Modified, with permission, from Morgan GE, Mikhail MS, Murray MJ., *Clinical Anesthesiology*, 4th ed. New York: McGraw-Hill, 2006.)

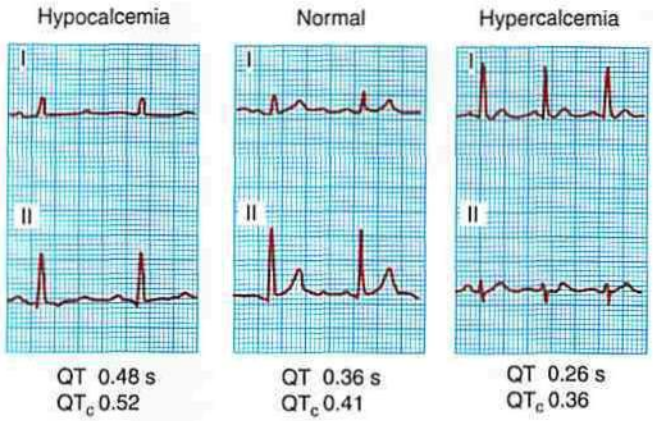


FIGURE 8-46. Electrocardiographic effects of hypocalcemia and hypercalcemia. Prolongation of the QT interval (ST-segment portion) is typical of hypocalcemia. Hypercalcemia may cause abbreviation of the ST segment and shortening of the QT interval. (Modified, with permission, from Kasper DL, Braunwald E, Fauci AS, et al., eds, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 1319.)

Treatment

Treat the underlying cause. If patients are symptomatic, hydrate with **IV normal saline** and give **furosemide** with consideration given to the addition of **bisphosphonates**.

Hypocalcemia

Serum calcium level < 8.5 mg/dL.

Presentation

Frequently asymptomatic. More severe symptoms occur at very low serum levels: muscle cramps, depression, **tetany**, and convulsions. **QT segment prolongation** is seen on ECG (see Figure 8-59).

- **Chvostek's sign:** Tapping the facial nerve results in twitching of facial muscles.
- **Trousseau's sign:** Carpopedal spasm resulting from inflation of a BP cuff on the forearm.

Causes

In newborns and infants, consider **DiGeorge's syndrome**. Hypoparathyroidism (secondary to treatment of hyperparathyroidism), pseudohypoparathyroidism, vitamin D deficiency, osteomalacia, rickets, and diuretics (furosemide).

Treatment

If the patient is symptomatic, calcium can be replaced via **IV calcium gluconate** while monitoring ECG. Less severe cases can be treated with **PO calcium** and **vitamin D**.

Hypomagnesemia

Serum magnesium level < 1.5 mEq/L.

Presentation

Anorexia, nausea, vomiting, lethargy, and personality changes. Also look for hypocalcemia and hypokalemia in the setting of low magnesium levels. It is

often difficult to correct these electrolyte abnormalities when the others are present.

Causes

Dietary deficiency complicated by poor absorption.

Treatment

Low magnesium is treated with magnesium replacement, usually magnesium sulfate.

Pharmacology

DIURETICS

Diuretics (see Figure 8-47) are drugs that act to **increase urine volume** by altering ion transport in the nephron. A generally safe class, diuretics are **first-line drugs** in the treatment of **hypertension and edematous states** such as **congestive heart failure (CHF), nephrosis, and cirrhosis.**

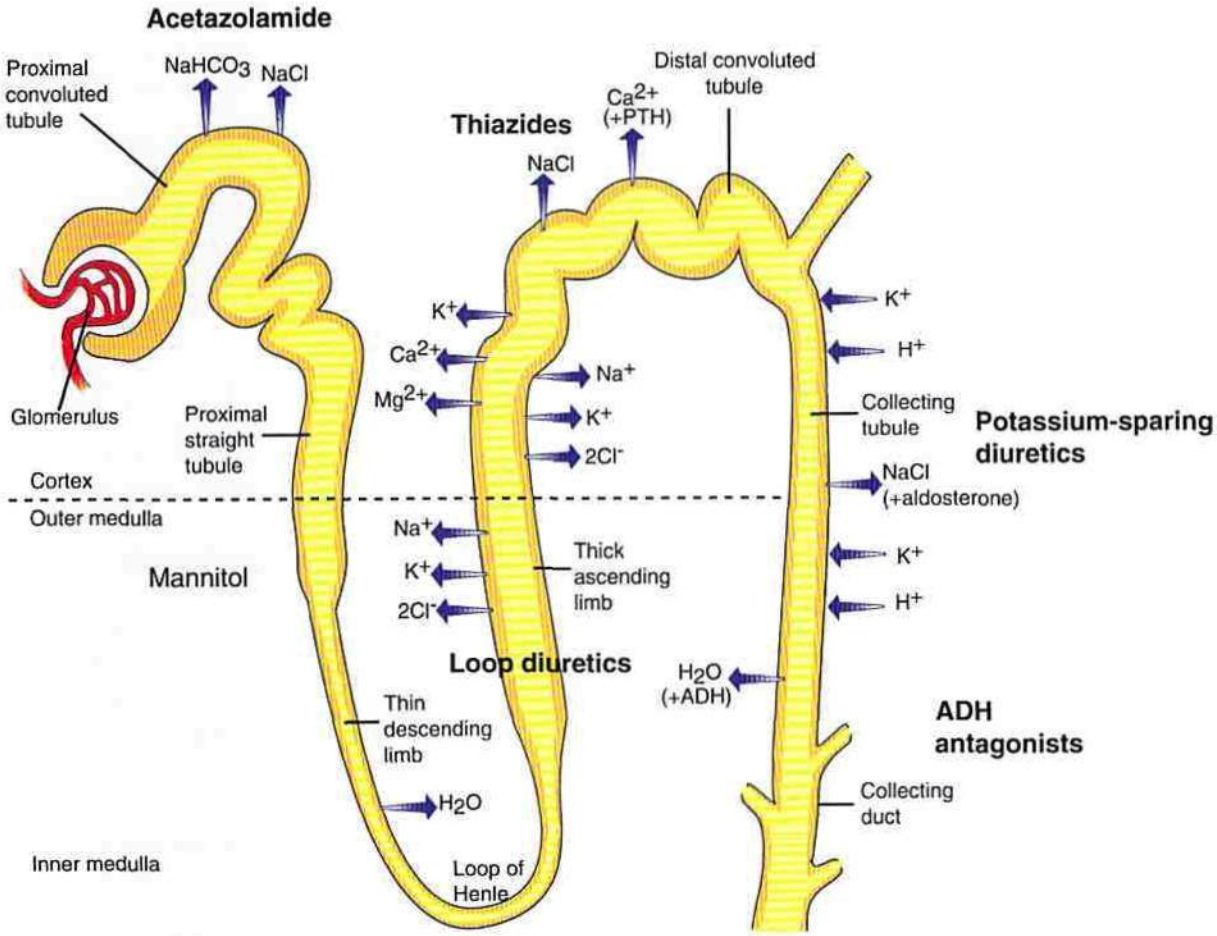


FIGURE 8-47. Overview of diuretic sites of action. (Modified, with permission, from Katzung BG, *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton and Lange, 1997: 243.)

Common side effects of diuretics (see Table 8-21) are:

- Volume depletion.
- Hypokalemia (loop diuretics and thiazides).
- Hyponatremia (thiazides).
- Hyperglycemia (thiazides).
- Metabolic alkalosis (acetazolamide).
- Specific side effects are discussed with each drug class below.

There are **five main classes** of diuretics:

- Osmotic agents: Mannitol and urea.
- Carbonic anhydrase inhibitors: Acetazolamide.
- Loop agents: urosemide, bumetanide, and ethacrynic acid.
- Thiazides: Hydrochlorothiazide (HCTZ) and metolazone.
- Potassium-sparing agents: Spironolactone, triamterene, and amiloride.

Osmotic Agents (Mannitol and Urea)

Mechanism

Mannitol is filtered into the tubular lumen but not reabsorbed, increasing osmotic pressure in the lumen.

TABLE 8-21. Common Electrolyte Changes Seen with Diuretic Use

Class	Drugs	Mechanism of Action	Electrolyte Changes
Carbonic anhydrase inhibitors	Acetazolamide	Inhibits carbonic anhydrase in PCT, blocks Na^+/H^+ exchange.	▪ Hyperchloremic metabolic acidosis ($\uparrow Cl^-$, $\uparrow H^+$) ▪ Hypokalemia ($\downarrow K^+$)
Osmotic agents	Mannitol, urea	Increases tubular fluid osmolarity in entire tubule.	▪ Hypernatremia ($\uparrow Na^+$)
Loop agents	Furosemide, bumetanide, ethacrynic acid	Inhibits Na^+-K^+-$2Cl^-$ transporter in thick ascending limb of loop of Henle.	▪ Hyperchloremic metabolic acidosis ($\uparrow Cl^-$, $\uparrow H^+$) ▪ Hyperuricemia ($\uparrow$urea) ▪ Hypokalemia ($\downarrow K^+$) ▪ Hypocalcemia ($\downarrow Ca^{++}$) ▪ Hypomagnesemia ($\downarrow Mg^{++}$)
Thiazide diuretics	Hydrochlorothiazide, chlorothiazide	Blocks Na^+-Cl^- co-transport in DCT.	▪ Hyperglycemia ($\uparrow$glucose) ▪ Hyperlipidemia ($\uparrow$lipids) ▪ Hyperuricemia ($\uparrow$urea) ▪ Hypercalcemia ($\uparrow Ca^{++}$) ▪ Hypochloremic metabolic alkalosis ($\downarrow Cl^-$,$\downarrow H^+$) ▪ Hypokalemia ($\downarrow K^+$) ▪ Hyponatremia ($\downarrow Na^+$)
Potassium-sparing agents	Spironolactone, amiloride, triamterene	▪ Spironolactone is a competitive aldosterone receptor antagonist in collecting tubule. ▪ Other agents block Na^+ channels in collecting tubule.	▪ Metabolic acidosis ($\uparrow H^+$) ▪ Hyperkalemia ($\uparrow K^+$)

Uses

Reduction of intraocular or intracranial pressure, increases excretion of water with lesser sodium loss effects, urinary excretion of metabolic toxins.

Side Effects

- Dehydration without adequate water intake.
- Increased ECF volume leading to pulmonary edema.

Carbonic Anhydrase Inhibitors (Acetazolamide)

Mechanism

Blocks carbonic anhydrase, primarily in proximal tubule, preventing reabsorption of sodium bicarbonate, leading to diuresis.

Uses

Glaucoma (decreases production of aqueous humor), acute mountain sickness (stimulates respiration by inhibiting carbonic anhydrase acidosis), elimination of acidic toxins (alkalinizes urine, leading to increased excretion of weak acids), and corrects metabolic alkalosis in CHF or respiratory acidosis.

Side Effects

- Renal stones (increases urine concentration of Ca^{2+} and phosphates).
- Potassium wasting (increased HCO_3^- in tubules attracts K^+).
- Hyperchloremic metabolic acidosis.

KEY FACT

Acetazolamide is **contraindicated** in **patients allergic to sulfonamides,** since they share the **sulfa group ($R–SO_2–NH_2$).**

MNEMONIC

The **AM** is the **proximal part of the day.**
Acetazolamide and **M**annitol act on the **proximal tubule.**

Loop Agents (Furosemide, Bumetanide, and Ethacrynic Acid)

Mechanism

Inhibit $Na^+–K^+–2Cl^-$ transporter in thick ascending limb. Decreases positive luminal potential leading to increased excretion of calcium and magnesium.

Uses

Treatment of acute pulmonary or other edema, hypercalcemia, hyperkalemia, and ARF.

Side Effects

- Hypokalemic metabolic alkalosis
- Ototoxicity
- Hyperuricemia
- Hypomagnesemia
- Severe dehydration
- Allergic reactions (sulfonamide derivatives)

CLINICAL CORRELATION

Ethacrynic acid may be used in patients allergic to sulfonamides.

Ethacrynic acid is a loop agent that acts on the same $Na^+–K^+–2Cl^-$ transporter, **but is not a sulfonamide derivative** like furosemide and bumetanide.

Thiazide Diuretics (Hydrochlorothiazide [HCTZ] and Metolazone)

Mechanism

Inhibit $Na^+–Cl^-$ co-transport in DCT.

Uses

Treatment of hypertension, CHF, nephrosis, and hypercalciuria, and nephrogenic DI (thiazides produce hyperosmolar urine, thereby diminishing polyuria).

Side Effects

- Dehydration
- Hypokalemia
- Hypochloremic metabolic alkalosis
- Hypercalcemia
- Hyperglycemia
- Hyperlipidemia
- Hyperuricemia
- Hyponatremia
- Allergic reactions (sulfonamide derivatives)

Potassium-Sparing Agents (Spironolactone, Amiloride, and Triamterene)

Mechanism

Spironolactone directly antagonizes MRs (aldosterone), thereby preventing Na^+ reuptake. Amiloride and triamterene directly inhibit Na^+ channels, preventing movement of K^+ into the tubular lumen.

Uses

- **Spironolactone:** Primary hyperaldosteronism (Conn's syndrome) and edematous states caused by secondary aldosteronism (cirrhosis, nephrotic syndrome, and cardiac failure).
- **Amiloride and triamterene:** Counteract K^+ loss caused by other diuretics, adjunct to other diuretics to treat edema or hypertension.

FLASH BACK

Spironolactone is a synthetic 17-lactone steroid with **anti-androgen activity**; binds and blocks the androgen receptor, resulting in **gynecomastia.**

Side Effects

Hyperkalemia, hyperchloremic metabolic acidosis, gynecomastia, impotence (males), abnormal menses (females).

ANTIDIURETIC HORMONE (ADH) (VASOPRESSIN AND DESMOPRESSIN)

Mechanism

Upregulates selective water channels in collecting tubules.

Uses

Central DI, enuresis.

Side Effects

- Vasoconstriction
- Headache
- Nausea

ANTIDIURETIC HORMONE ANTAGONISTS

Demeclocycline

Mechanism

Nonselectively inhibits action of ADH in collecting tubule through decrease of cAMP.

Uses

SIADH, decrease intravascular fluid volume in heart or liver failure.

Side Effects

- Nephrogenic DI
- Renal failure

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Lisinopril, Enalapril, Captopril, and Ramipril

Mechanism

Inhibit ACE, which catalyzes conversion of angiotensins I to II, interrupting the renin–angiotensin–aldosterone axis. Also **increases** levels of **bradykinin** (a potent vasodilator). In the kidney, ACE inhibitors decrease efferent arteriolar resistance, improving glomerular blood flow.

Uses

Treatment of mild to moderate hypertension. Proven renal protective function in diabetics (decreases proteinuria and improves renal function in diabetic nephropathy).

Side Effects

- Dry cough (due to increased levels of bradykinin).
- Teratogenic (do not give to pregnant women).
- Hypotension.
- Acute renal failure (patients with bilateral renal artery stenosis).
- Hyperkalemia.
- Angioedema.

ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

Losartan, Candesartan, Irbesartan, and Valsartan

Mechanism

Block vasoconstriction and aldosterone-producing effects of angiotensin II at receptor sites in vascular smooth muscle and adrenal glands, interrupting the renin–angiotensin–aldosterone axis. **Unlike ACE inhibitors**, ARBs **do not affect bradykinin**, thus are rarely associated with the persistent dry cough and/or angioedema that limit ACE inhibitor therapy.

Uses

Treatment of mild to moderate hypertension. Alternative drug therapy for patients who cannot tolerate ACE inhibitors.

Side Effects

- Hypotension
- Teratogenic (do not give to pregnant women)
- Acute renal failure
- Hyperkalemia

NEPHROTOXIC DRUGS

The kidneys are critical organs for removal of most drugs from the body. Table 8-22 lists commonly used drugs and frequently encountered toxins that impair renal function.

TABLE 8-22. Common Renal Manifestations of Adverse Drug Reactions and Toxins

Drug Class	Common Drugs	Toxic Renal Action(s)
Antihypertensives	ACE inhibitors, ARBs.	Fetal renal toxicity (teratogenic).
Antibiotics	Aminoglycosides (e.g., gentamycin, neomycin), penicillins (esp. methicillin), β-lactams, sulfonamides (e.g., sulfamethoxazole), trimethoprim, rifampin.	Mild renal impairment to acute tubular necrosis (ATN) or acute interstitial nephritis (AIN).
Antivirals	Acyclovir, ganciclovir, foscarnet.	Transient renal dysfunction.
Antifungals	Amphotericin B, polymyxin.	Dose-related nephrotoxicity (direct acute tubular injury).
Anti-inflammatory	NSAIDs (e.g., ibuprofen, indomethacin, naproxen), COX-2 inhibitors (e.g., rofecoxib).	▪ AIN, renal papillary necrosis, direct tubular injury due to ischemia. ▪ Inhibition of COX isoenzymes inhibits renal PGI_2 production, leading to altered excretion of Na^+, edema, and hypertension.
Immunosuppressive drugs	Cyclosporine, tacrolimus (FK506).	Dose-related nephrotoxicity (direct acute tubular injury).
Chemotherapy drugs	Cisplatin, cyclophosphamide.	Dose-related nephrotoxicity, hemorrhagic cystitis.
Radiocontrast dyes	Iodinated contrast agents.	Contrast-induced acute renal failure(CIARF), usually in patients with underlying renal disease (e.g., diabetics).
Endogenous toxins	Myoglobin (rhabdomyolysis), hemoglobin (hemolysis).	ATN, oliguria.
Other exogenous toxins	Ethylene glycol.	Renal failure at high doses.
	Heavy metals (i.e., arsenic, lead).	ATN, oliguria.

CLINICAL CONSIDERATIONS

Administration of any drug requires careful monitoring to ensure that desired therapeutic affects are achieved without unacceptable adverse effects. Patients taking antihypertensive drugs typically are older, have comorbid diseases, and take multiple medications. Table 8-23 identifies common comorbid states that require cautious monitoring of renal function and careful attention to concomitant drug use due to their effects on pharmacokinetics, drug metabolism, and water and solute balance.

TABLE 8-23. Antihypertensive Drug Use in Common Comorbid Medical Conditions

Comorbid Medical Conditions	Diuretic Use	ACE Inhibitors/ ARBs	Other Drugs Commonly Used to Treat Condition
Diabetes		First-line agents	β-Blockers, lipid-modifying agents, calcium channel blockers, oral hypoglycemic drugs, and insulin.
Hyperlipidemia			Frequent comorbid condition with diabetes and heart disease.
Chronic kidney disease (CKD)	First-line agents	Alternative agents	
Congestive heart failure (CHF)	First-line agents	First-line agents	β-Blockers and other antiarrhythmic agents, lipid-modifying agents.
Previous myocardial infarction (MI)	Alternative agents	First-line agents	β-Blockers and other anti-arrhythmic agents, lipid modifying agents.
Angina pectoris	Alternative agents	Alternative agents	β-Blockers and other anti-arrhythmic agents, lipid modifying agents.
Chronic obstructive pulmonary disease (COPD)	First-line agents	Alternative agents	Theophylline, sympathomimetics (i.e., albuterol), anticholinergic drugs, inhaled corticosteroids, ipratropium.

Rapid Review

Key Terms

ARF	Sudden decline in renal function (triggered by numerous disease processes).
Anuria	Absence of urine production.
Azotemia	Accumulation of nitrogenous waste products (BUN and creatinine) in the blood.
Dysuria	Painful or difficult urination.
Hematuria	Presence of blood in the urine.
Nocturia	Excessive urination at night.
Oliguria	Diminished urine output (< 0.5 mL/kg/h).
Polydipsia	Excessive thirst (may signal diabetes).
Renal colic	Severe, intermittent pain originating in the flank and radiating to the groin, often attributed to presence of a kidney stone in the collecting system.
Uremia	Excess of the nitrogen waste products of protein in the blood with the signs and symptoms of chronic renal failure (CRF).

NEPHROTIC SYNDROME

Proteinuria (> 3.5 g/d), hypoalbuminemia, generalized edema, hyperlipidemia and lipiduria resulting from damage to the capillary walls of the glomeruli. Loss of protein in the intravascular space will lead to severe edema (anasarca), hypoperfused kidneys, and activation of the renin–angiotensin–aldosterone system (RAAS).

Minimal Change Disease

Most frequent in **children** aged 2–3 years. Children present with generalized edema, particularly **periorbital edema**. Light microscopy shows normal-appearing glomeruli, while electron microscopy (EM) shows loss of visceral epithelial podocytes (**foot process effacement**). The protein lost in the urine is mostly albumin (**selective proteinuria**). Responds well to **steroids**.

Membranous Glomerulonephritis

Most common in those **30–50 years old**. The cause is diffuse thickening of the GBM due to subepithelial deposits separated by small spikes of GBM matrix (**spike-and-dome pattern**). There is a loss of globulins as well as albumin (**nonselective proteinuria**).

Focal Segmental Glomerulosclerosis

This is a frequent cause of nephrotic syndrome in immunocompromised patients (**HIV/AIDS**). On kidney biopsy, segments of only some of the glomeruli show sclerosis and deposits of hyaline (**hyalinosis**). In addition to the presentation of characteristic nephrotic syndrome, patients may also have **mild hematuria and hypertension**. Proteinuria is nonselective.

Membranoproliferative Glomerulonephritis

There are two types. **Type I** is characterized by subendothelial electron-dense deposits and accounts for most cases. These deposits give the GBM a "**double contour**" or **tram-track** appearance. Those with **type II** commonly have **C3 nephritic factor**.

NEPHRITIC SYNDROME

Hematuria with RBCs in the urine, **oliguria or azotemia (elevated BUN and Cr)**, and **hypertension**. There are four common diseases that cause this syndrome, each characterized by injury to the capillary walls permitting escape of RBCs into the urine. See Table 8-24 for comparison of nephrotic and nephritic syndromes.

Acute Proliferative Glomerulonephritis

Patients present with **smoky brown-colored urine**, hypocomplementemia, and IgG deposits on the GBM. These deposits are subepithelial (**subepithelial humps** on EM) and cause an intense inflammatory reaction. The antigen of the antigen-antibody complexes is usually from a preceding **post-streptococcal infection**.

Rapidly Progressive (Crescentic) Glomerulonephritis

Loss of renal function within **days to weeks**, and is manifest by **active urine sediment** (hematuria, dysmorphic RBCs, and RBC casts). Histologically, it is

TABLE 8-24. Nephrotic versus Nephritic Syndrome

	Nephrotic Syndrome	Nephritic Syndrome
Cause	Increased permeability of the GBM, leading to massive proteinuria and secondary metabolic changes.	Inflammation of the glomerulus, with resultant rupture of glomerular capillaries, causing hematuria.
Proteinuria	Yes, > 3.5 g/24 h.	Variable, usually < 1.5 g/24 h.
Edema	Yes, often massive.	Variable, usually mild.
Hypoalbuminemia	Yes, secondary to renal loss.	No.
Hypertension	Variable.	Yes.
Hyperlipidemia	Yes, secondary to increased hepatic production.	No.
Hematuria	Variable.	Yes, often macroscopic; smoky-*brown urine.*

characterized by the formation and proliferation of parietal cells and monocytes (forming **crescents**) between Bowman's capsule and the glomerular tuft.

IgA Nephropathy (Berger's Disease or Focal Glomerulonephritis)

Nephritic syndrome caused by the deposition of IgA (due to abnormal production and clearance) in the mesangium. It usually affects **young children** and clinically manifests as gross, **recurrent hematuria following an upper respiratory infection**. It can exist alone, or as a component of **Henoch-Schönlein purpura** (Berger's disease with a systemic syndrome involving a purpuric rash, abdominal pain, and arthritis).

Alport's Syndrome

Affects males 20–50 years old and is **nephritic syndrome** accompanied by **nerve deafness** and various **eye disorders** (lens dislocation, posterior cataracts, and corneal dystrophy).

URINARY TRACT INFECTIONS

Classically presents with **dysuria** (pain with urination), increased **frequency** of urination, and a **sense of urgency** caused by irritation of the **bladder and urethra** by bacterial infection. The most common offending bacteria are ***Escherichia coli*** as well as *Proteus* and *Klebsiella*. It is more frequently seen in **women** due to a shorter urethra, and can be diagnosed with a urinalysis showing **bacteriuria**, positive **leukocyte esterase**, and positive **nitrites**.

Acute Pyelonephritis

A bacterial infection of the kidney that mainly targets the renal pelvis and almost always involves infection of the lower urinary tract as well. Signs that the kidney is also involved include **flank pain** and **pyuria** (WBCs in the

urine). If the kidney becomes obstructed and is unable to drain the infection, the renal pelvis may fill with a suppurative exudate, producing **pyonephrosis**.

Vesicoureteral Reflux

A congenital defect, present in up to 40% of children with a UTI, resulting in incompetent ureterovesicular valves which allow infected bladder urine to reflux back up into the renal pelves. Suspect this in **young children** (especially young males) with **recurrent UTIs**.

Chronic Reflux Nephropathy

The most common form of chronic pyelonephritis and results from a UTI with congenital **VUR**. This can lead to chronic renal insufficiency if left untreated when patients present later in life with hypertension and renal insufficiency.

URINARY TRACT INSULTS

Necrotizing Papillitis/Papillary Necrosis

A form of pyelonephritis characterized by ischemic and suppurative necrosis of the renal papillae (more common among **diabetics** and those who **abuse aspirin or acetaminophen**). Gray to yellow necrosis of the renal pyramids is pathognomonic for this disease.

Acute Drug-Induced Interstitial Nephritis

An adverse drug reaction that begins about a couple weeks after exposure. It is characterized by **fever, eosinophilia, rash,** rising serum creatinine, and possibly **ARF**. Stopping the offending agent early is usually curative.

Acute Tubular Necrosis

The most common cause of ARF presenting as **oliguria** and **muddy brown casts** in the urine. It is caused by destruction of tubular epithelial cells from renal ischemia due to shock, trauma, bacterial sepsis, or exposure to nephrotoxic agents.

CYSTIC KIDNEY DISEASE

Simple Cysts

Less than **5 cm** in size, these cysts are usually filled with clear fluid and confined to the **cortex** of the kidney. These can be differentiated from tumors by ultrasound findings of smooth contours, lack of vascularity, and positive fluid signals.

Dialysis-Associated Acquired Cysts

Dialysis patients may present with **hematuria** after many years of treatment. These cysts occur in both the medulla and the cortex and may become a place for **renal adenomas** to form.

Autosomal Dominant Polycystic Kidney Disease (ADPCKD)

Patients usually present in their **40s** with **flank pain**, intermittent **hematuria**, a palpable abdominal/flank mass, and a positive **family history** of kidney disease. ADPCKD is characterized by multiple cysts in both kidneys that destroy the intervening parenchyma. It accounts for 10% of CRF and is a cause of

refractory hypertension and urinary infection. There is an association with **saccular aneurysms** affecting the circle of Willis, leading to a high incidence of **subarachnoid hemorrhage**.

Autosomal Recessive (Childhood) Polycystic Kidney Disease (ARPCKD)

Rare, autosomal recessive, developmental disease subgrouped into four types: perinatal, neonatal, infantile, and juvenile. All result from mutations on chromosome 6p. Serious illness presents at birth, and death may follow due to renal or pulmonary failure. Grossly, the kidneys are affected bilaterally and take on a sponge-like appearance. Patients who survive develop cysts in the liver and ultimately develop congenital hepatic cirrhosis.

VASCULAR DISEASES AND THE KIDNEY

Benign Nephrosclerosis

Occurs after years of "benign" hypertension with a slow decrease in kidney function and proteinuria. It is associated with hyaline thickening of the walls of the small arteries within the kidney, resulting in decreased blood flow and ischemia. This results in the kidneys being symmetrically atrophic with a granular surface.

Malignant Hypertension

Presents clinically as **diastolic pressures > 120 mmHg** and ultimately renal failure with **symptoms of end-organ damage** such as headache, nausea, and visual impairment. It may occur in people with or without prior hypertension due to dysfunction of the renin-angiotensin system. The high BP damages vessel walls and increases fibrin permeability (**fibrinoid necrosis**). Inflammatory cells are also present due to the vascular damage (**necrotizing arteriolitis**).

THROMBOTIC MICROANGIOPATHY

A group of syndromes that present with microangiopathic hemolytic anemia, thrombocytopenia, and sometimes renal failure due to widespread thrombosis in the microvasculature.

Hemolytic Uremic Syndrome (HUS)

Presents with **GI and flu-like symptoms** followed by bleeding problems (**hematuria**), and usually follows intestinal infection with Shiga toxin–producing bacteria (***E. coli* O157:H7**), which causes endothelial damage, and thus increasing thrombosis and vasoconstriction, particularly in the kidney. It is one of the main causes of **ARF in children**.

Thrombotic Thrombocytopenic Purpura (TTP)

Presents with the classic pentad of fever, anemia, thrombocytopenia, renal dysfunction, and some form of neurologic deficit. It is caused by an acquired defect in proteolytic cleavage of vWF multimers.

RENAL STONES (NEPHROLITHIASIS)

Stone formation at any level in the urinary system, usually due to an increase in urine concentration, with most composed of **calcium oxalate**. They present with flank pain radiating to the groin (**renal colic**) and possibly **hematuria**.

- **Hydroureter:** If a stone descends into the ureter, it may cause an obstruction, leading to accumulation of fluid behind the stone and dilation of the ureter and even the renal pelvis.
- **Hydronephrosis:** Obstruction leading to dilation of the renal pelvis and with subsequent atrophy of the parenchyma due to back pressure on the kidney.

Magnesium Ammonium Phosphate (Struvite)

These almost always occur in patients with persistently alkaline urine due to UTIs, especially with ***P. vulgaris*** (a urease-positive organism).

Uric Acid Stones

Gout and disease leading to rapid cell turnover induce high uric acid levels in the urine with the possibility of uric acid stone formation.

Cysteine Stones

Associated with a genetically determined defect in the renal transport of amino acids (cysteine).

Staghorn Calculi

Accretion of salts leads to the development of these branching structures which create a cast of the renal pelvis and calyx system.

ELECTROLYTE ABNORMALITIES

Electrolyte abnormalities are frequent clinical occurrences. The presenting symptoms are determined by the electrolyte involved. See Table 8-25 for a review.

ACUTE RENAL FAILURE

Acute renal failure most commonly presents with a decrease in kidney function manifested as decreased urine output (**oliguria**) with an increase in the accumulation of nitrogenous waste products (**azotemia**). The cause of ARF can be classified by the location of the insult: before, after, or within the kidney (see Table 8-26).

TUMORS OF THE RENAL SYSTEM

Renal Cell Carcinoma

Presents most commonly in men over the age of 60 who have a history of smoking, cadmium exposure, and chronic dialysis. The classic triad of symptoms includes **hematuria, fever, and dull flank pain**. It may also cause symptoms of **polycythemia** from the production of epoetin alfa. Three types exist.

- **Clear cell (most common):** Tumor cells have clear cytoplasm. The underlying genetic defect is in the ***VHL* gene**, a tumor suppressor gene.
- **Papillary:** Tumor cells show a papillary growth pattern and affect the proximal tubule. The underlying genetic defect involves the ***MET* proto-oncogene** on chromosome 7.
- **Chromophobic:** Tumor cells stain more darkly than clear cells and affect the cortical collecting ducts. They are characterized by **loss of an entire chromosome**. Good prognosis.

TABLE 8-25. Electrolyte Abnormalities

	Presentation	Causes
Hypernatremia	Excessive thirst, **doughy skin**, and mental status changes.	Hypertonic saline, diuretics, diabetic ketoacidosis, and central or nephrogenic DI.
Hyponatremia	Headaches, nausea, muscle cramps, depressed reflexes, and disorientation.	Skin or GI losses, **SIADH**, water intoxication, and liver or heart failure; beware of **central pontine myelinolysis** during correction.
Hyperkalemia	Palpitations, muscle weakness; peaked T waves, widened QRS interval, flattened P waves, ventricular fibrillation.	Lab error (hemolysis), renal failure, crush injury.
Hypokalemia	Fatigue, muscle weakness, hyporeflexia; flattened T waves, U waves, ST-segment depression.	Insulin, diuretics, vomiting, hyperaldosteronemia, hypomagnesemia.
Hypercalcemia	"Renal stones, abdominal moans, painful bones, and psychiatric overtones".	Malignancy, hyperparathyroidism, granulomatous disease.
Hypocalcemia	Muscle cramps, depression, tetany, convulsions; QT-segment prolongation; Chvostek's and Trousseau's signs.	DiGeorge's syndrome (in children), hypoparathyroidism (following parathyroidectomy), furosemide, and vitamin D deficiency.
Hypomagnesemia	Often asymptomatic; anorexia, nausea, vomiting, lethargy.	Dietary deficiency; difficult to correct hypocalcemia or hypokalemia in the setting of hypomagnesemia.

Urothelial (Transitional) Cell Carcinoma

Tumors of the lower urinary tract are more common than renal cell carcinomas, and frequently present with **painless hematuria**. Men 50–70 years old are more frequently affected. There may be prior exposure to β-naphthylamine, cigarette smoking, and schistosomiasis.

Wilms' Tumor

This is the **most common tumor in children** (peak incidence between 2 and 4 years old). It usually presents with a **palpable flank mass** that originates from primitive metanephric tissue. It is composed of a variety of cells. Geneti-

TABLE 8-26. Types of Renal Failure

Variable	Prerenal	Renal	Postrenal
Urine osmolality	>500	<350	<350
Urine Na	<10	>20	>40
Fe_{Na}	<1%	>2%	>4%
BUN/Cr ratio	>20	<15	>15

cally, it is often associated with deletions of the short arm of **chromosome 11** (*WT-1* and *WT-2* cancer suppressor genes are located here).

AUTOIMMUNE RENAL DISEASES

Goodpasture's Syndrome

Nephritic syndrome caused by anti-GBM antibodies (targeting a component of type IV collagen) that also affect the lung alveoli. The result is both lung and kidney lesions manifested as **hematuria with hemoptysis**.

Wegener's Nephritis

Small-vessel vasculitis involving the upper and lower respiratory tract with glomerulonephritis. Histopathologically, it causes necrotizing inflammation and granuloma formation in small arteries and veins. Respiratory involvement presents as paranasal sinus pain, drainage of bloody nasal discharge, hemoptysis, dyspnea, or chest discomfort. ANCA-**positive** in 80% of patients with renal involvement. Biopsy shows focal segmental glomerulonephritis.

CHAPTER 9

Reproductive

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KEY FACT

Most disorders of sexual differentiation involve discordance between the gondal and genital sex, leading to **pseudohermaphroditism**.

CLINICAL CORRELATION

The presence or absence of a Y chromosome determines the genetic sex, even in errors of sex chromosome nondisjunction. For example, individuals with Klinefelter's syndrome (47,XXY) are considered to be genetically male and those with Turner's syndrome (45,XO) are female.

KEY FACT

Steroid and peptide hormones secreted by the gonads lead to differentiation of the internal and external sexual structures and imprinting of the brain.

FLASH FORWARD

The physiologic effects of testosterone and anti-müllerian hormone (AMH) are critical for the expression of male phenotypic gender.

Embryology

REPRODUCTIVE DEVELOPMENT

Determination of Gender

The structural and functional aspects of human sexuality are determined in four steps:

- Genetic sex: Presence or absence of a Y chromosome.
- Gonadal sex: Presence of testes or ovaries.
- Phenotypic sex: Appearance of the external genitalia.
- Sexual identity: Composite of psychosocial influences on sexual behavior, orientation, and role.

Genotypic Gender

Genetic, or karyotypic, sex is determined at the time of conception. The oocyte provides an X chromosome, and the sperm cell carries either an X or Y chromosome. Thus, at fertilization, either an XX female or XY male is created. The **sex-determining region (SRY) gene** on the Y chromosome encodes the **testis-determining factor** (TDF), a transcription factor whose targets induce a male phenotype. In the absence of SRY or TDF, a female phenotype develops. Notably, the genes from both X chromosomes are needed for female development, but can be overridden by SRY.

Phenotypic Gender

Additionally, gender phenotype is affected by hormonal expression (see Table 9-1). While the **female phenotype is the default,** the male phenotype requires expression of testosterone by the interstitial Leydig's cells and anti-müllerian hormone (AMH) by Sertoli's cells.

Early Indifferent Development

The *SRY* gene is not activated until the seventh week of embryonic development, so reproductive organs undergo an initial common stage of development beginning in the fifth week, known as the **indifferent stage.** Male and female external genitalia can be differentiated by **week 9** of fetal life and are

TABLE 9-1. Hormones in Sexual Differentiation

Hormone	Internal Structures	External Genitalia
Testosterone	Stimulates development of the vas deferens, seminal vesicles, and epididymis.	
MIF	Inhibits development of the ovaries and fallopian tubes.	
DHT	Stimulates development of the prostate.	Stimulates development of the penis and scrotum.
Estrogen		Stimulates development of the vagina and labia.

fully developed by **week 12**. For the male, the testes remain high in the abdomen until about the 30th week (seventh month) of gestation, when, under the influence of **müllerian-inhibiting factor (MIF)** and androgens (testosterone and dihydrotestosterone [DHT]), they undergo transabdominal and transinguinal descent, respectively.

Gonads

At the seventh week of gestation, if a Y chromosome is present, sex-determining region Y (*SRY*) leads to the development of testes; absence of *SRY* leads to formation of ovaries. Determination of the gonadal sex (i.e., formation of either testes or ovaries) leads to differentiation of the germ cells. In male development, Leydig's and Sertoli's cells develop by week 8, producing testosterone and MIF, respectively.

Primordial germ cells, which will form the gametes, migrate out to the yolk sac wall during gastrulation. As mitosis occurs during the fourth to sixth weeks, they return to the embryo through the GI tract and its surrounding peritoneum, the dorsal mesentery (see Figure 9-1). The cells **invade the gonadal ridge** (a mass of mesodermal tissue at the back of the abdominal cavity), proliferate, and become embedded medial to the developing mesonephros. Three primary cell types (mesenchymal cells, mesothelial cells, and primordial germ cells) develop in the gonadal ridge (see Table 9-2).

FLASH BACK

The development of the kidneys occurs in three stages. The **pronephros** (cervical region) is nonfunctional, the **mesonephros** (thoracolumbar region) functions temporarily, and the **metanephros** (pelvis) becomes the definitive kidney.

Genital Ducts

The **mesonephric (wolffian)** and **paramesonephric (müllerian)** ducts are mesodermal derivatives that form the male and female genital duct systems, respectively (see Figure 9-2). Testosterone stimulates differentiation of the wolffian duct, producing the epididymis, vas deferens, and seminal vesicle. Meanwhile, MIF blocks aromatase, thereby suppressing development of the müllerian duct. In females, the lack of these factors allows the müllerian duct to develop into the fallopian tubes and uterus, while the wolffian duct degenerates. An overview of these pathways is illustrated in Figure 9-3.

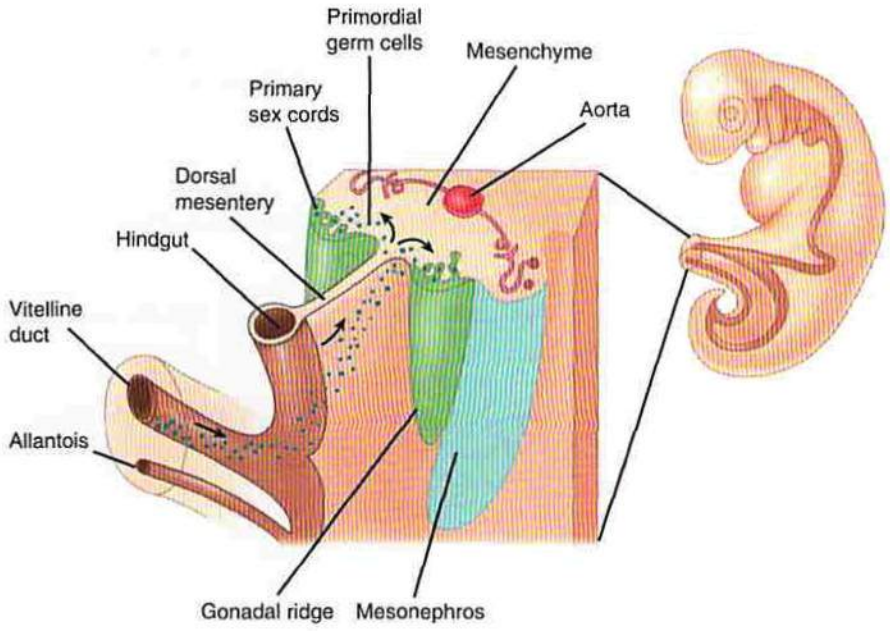


FIGURE 9-1. Primordial germ cell migration and gonadal ridge formation. The primordial germ cells migrate from the wall of the yolk sac to the gonadal ridge, where they settle into the primary sex cords.

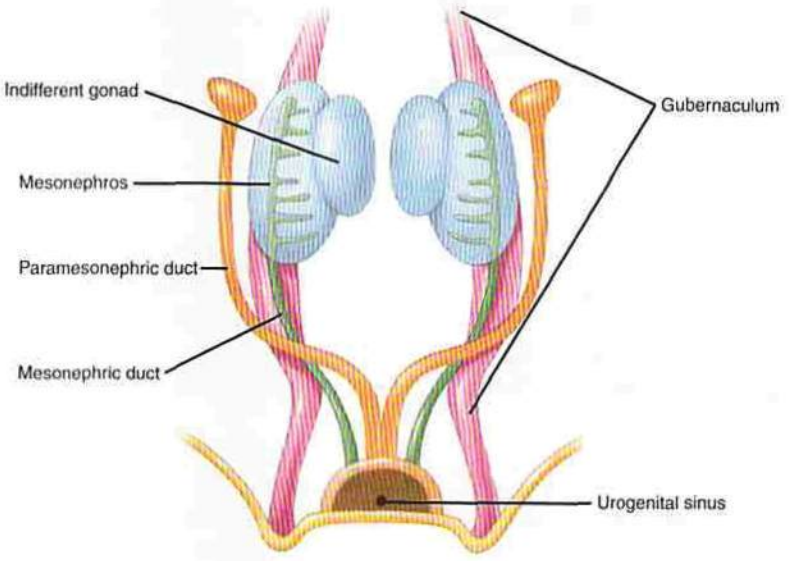


FIGURE 9-2. Indifferent genital duct formation. Once it becomes hollow, the mesonephric duct drains urine for the mesonephros. The paramesonephric duct forms lateral to the mesonephric duct and fuses at the midline. This fused tip will become the uterus.

FLASH BACK

Remember: The mesonephros, or primitive kidney, gives rise to the mesonephric (wolffian) duct. By contrast, the paramesonephric (müllerian) duct is not associated with any of the three steps of renal development.

The mesonephric duct is derived from intermediate mesoderm. It forms as a longitudinal solid cord of tissue dorsolateral to the mesonephric tubules in the thoracic region. The solid cords grow caudally and fuse with the ventrolateral walls of the cloaca, the urogenital sinus. Subsequently, it detaches from all but the urogenital sinus and canalizes, forming a lumen. During the sixth to 10th weeks it **drains urine from the mesonephros,** a temporary kidney.

The paramesonephric duct forms lateral to the mesonephric duct via an invagination of celomic epithelium on the cranial aspect of the mesonephros. The invaginated portion of the müllerian duct forms the ostium at the future fimbriated end (infundibulum) of the uterine tube, which opens into the celomic cavity, the future peritoneal cavity. The duct then grows caudally and crosses over the mesonephric duct. At the midline it fuses with the duct growing from the other side, forming a canal that will **become the uterus** (see Figure 9-3). The fused tip then presses on the urogenital sinus, forming a small protrusion.

FLASH BACK

If embryologic terms are giving you trouble, it may be worth reviewing the embryology decoder ring. As a brief review: meso = middle, para = alongside, caudal = hind part, cranial = head part.

TABLE 9-2. Gonadal Ridge Cell Types

Cell Type	Fate
Mesenchymal cells	Gonadal ridge medulla: Male = Leydig's cells; female = ovarian support stroma.
Mesothelial cells	Gonadal ridge and primary sex cord cortex: Male = seminiferous tubules; female = ovarian follicles.
Primordial germ cells	Enter primary sex cords as future gametes: Male = spermatogonia; female = oocytes.

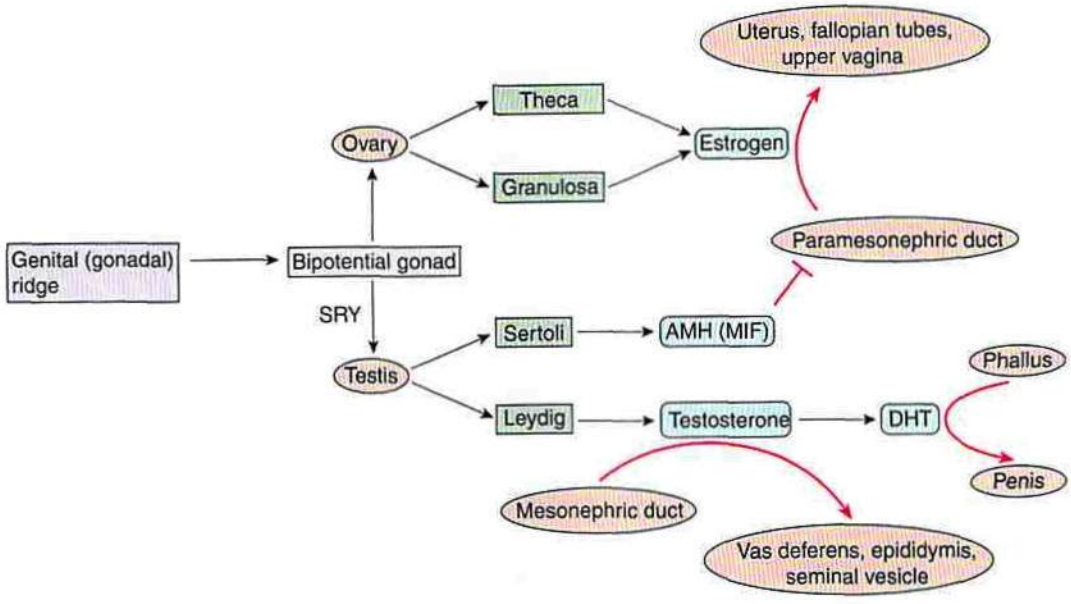


FIGURE 9-3. Overview of sexual differentiation. SRY = sex-determining region Y.

EXTERNAL GENITALIA

Masculinization (virilization) or feminization of the external genitalia also depends on the presence or absence of male hormones. Whereas testosterone mainly affects the internal structures, **DHT** affects the prostate, penis, and scrotum. In the female, lack of testes—and thereby vastly reduced levels of androgens—leads to development of the vagina and labia. Fetal estradiol has little effect on sexual differentiation, though estrogens from either the mother or exogenous sources can contribute to femininization of the genitalia in either gender. The roles of these hormones in determining gonadal and phenotypic sex are summarized in Table 9-1.

Around the fourth week, **five mesenchymal swellings** covered with ectoderm form around the cloacal membrane: one **genital tubercle**, two **urogenital folds**, and two **labioscrotal folds** (see Figure 9-4). The cloacal membrane divides in half and ruptures, forming the urogenital orifice and anus. A ligament, the **gubernaculum**, forms between the indifferent gonads and the labioscrotal swellings. This ligament will guide the testes into the scrotum and form the round ligaments of the uterus and ovaries.

KEY FACT

The **gubernaculum** holds the reproductive organs in place as the scrotal ligament in males and the round ligaments of the uterus and ovaries in females.

Male Development

TESTES

When the SRY gene is transcribed, its transcription factor product TDF acts on the indifferent gonads (see Figure 9-5). They differentiate into:

- Primary sex cords (middle): Coiled, solid **testis cords.**
- Primary sex cords (ends): Stay straight, join near hilum = **rete testes.**
- Rete testes + mesonephric tubule remnants: **Efferent ductules.**
- Mesenchyme thickening: **Tunica albuginea.**
- Mesothelial cells: **Sertoli's cells.**
- Mesothelial cells between testis cords: Interstitial cells (**Leydig's cells**).

The testes enlarge and separate from the mesonephros, following the lower gubernacula to reach the scrotum via the inguinal canal (see Figure 9-6). At

FLASH BACK

The **inguinal (Hesselbach's) triangle** *is the area defined by* the **rectus abdominis muscle** medially, the **inguinal ligament** inferiorly, and the **inferior epigastric vessels** superiorly and laterally. It is in this region that **direct inguinal hernias** protrude through the abdominal wall.

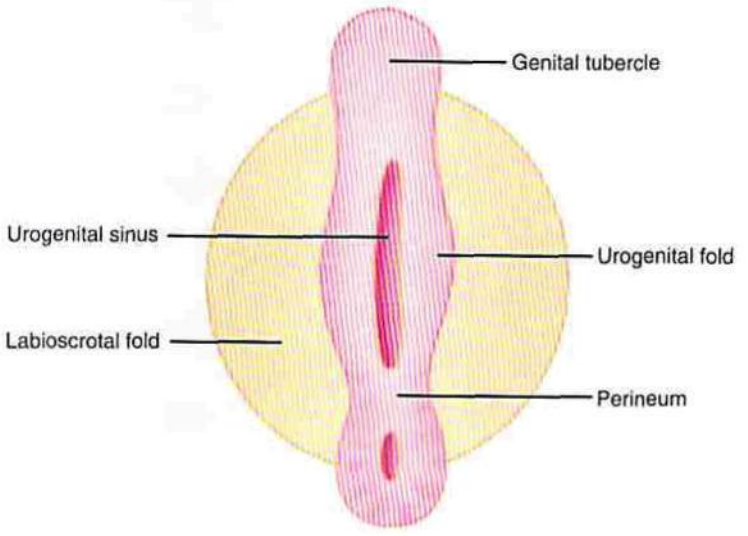


FIGURE 9-4. Indifferent external genitalia development. The indifferent external genitalia consist of five mesenchymal swellings: one genital tubercle, two urogenital folds, and two labioscrotal folds.

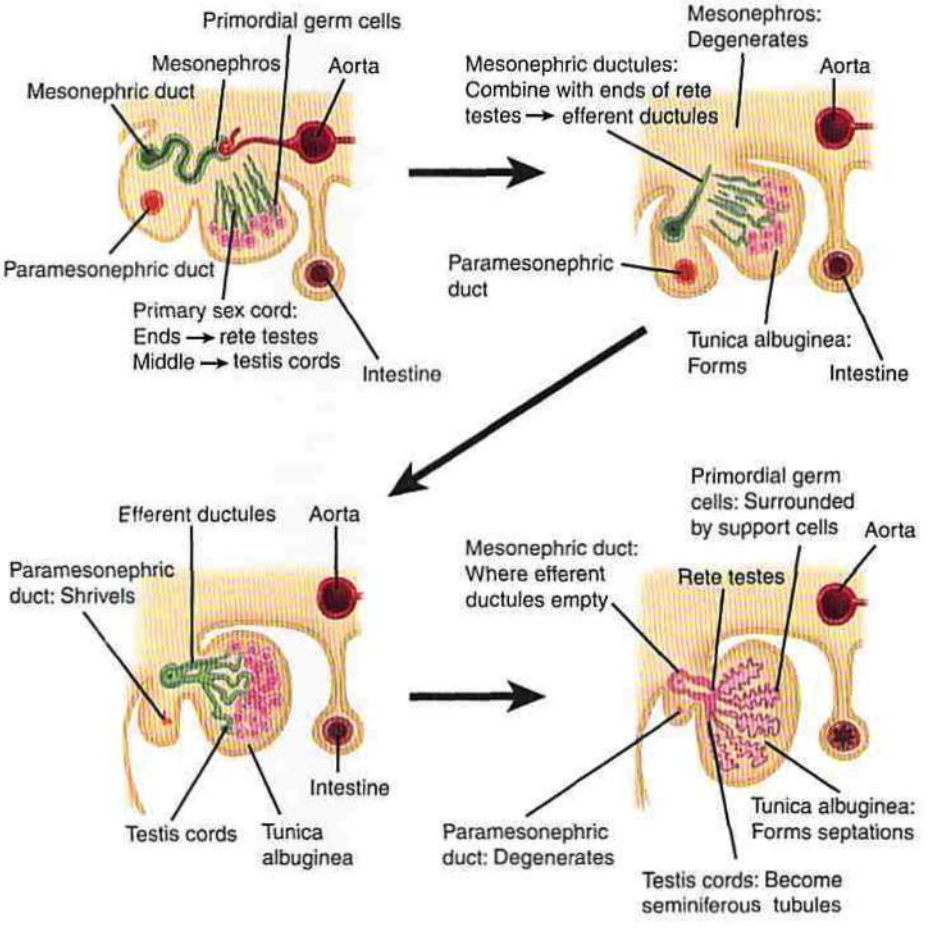


FIGURE 9-5. Testis development. As the testes develop, the testis cords, rete testes, and efferent ductules form, while the paramesonephric duct degenerates. As these structures mature, the tunica albuginea separates the testis cords whose mesothelial cells differentiate into Sertoli's and Leydig's support cells.

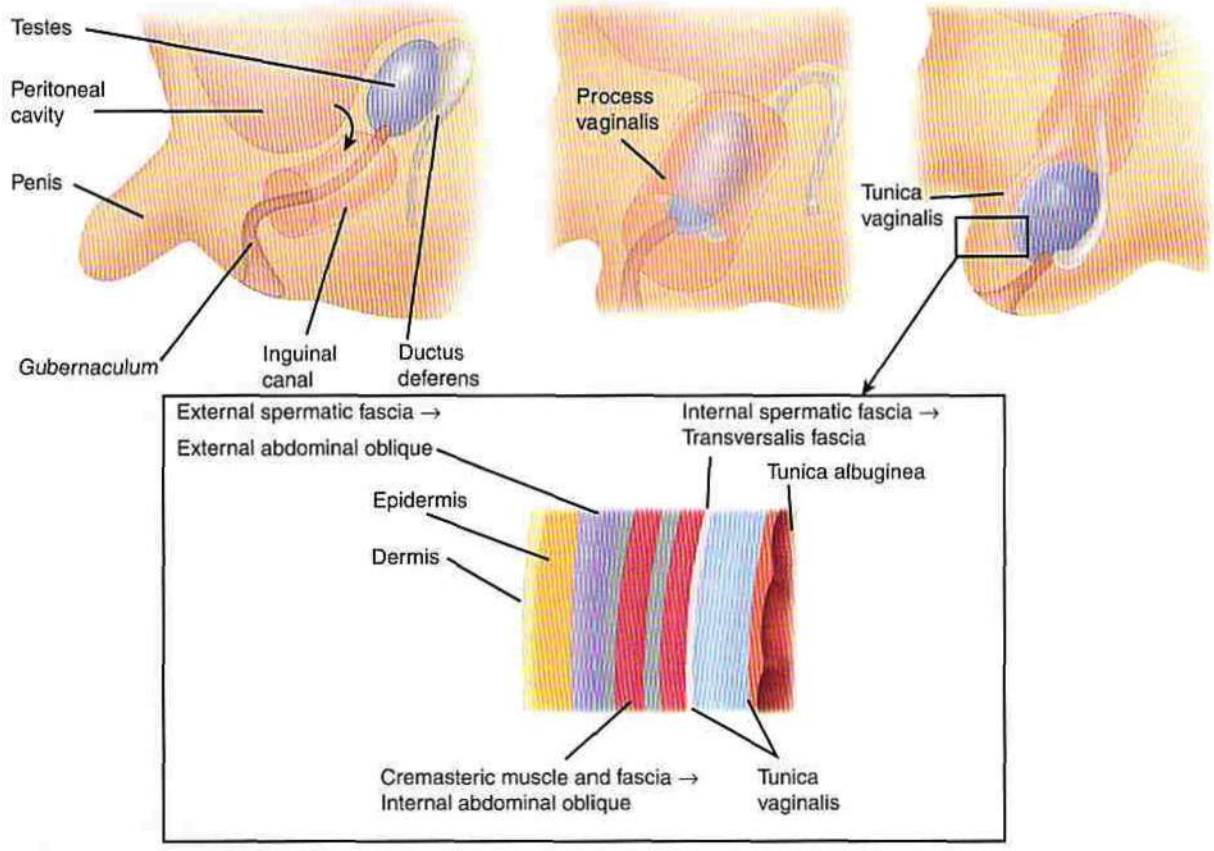


FIGURE 9-6. Male testicular descent. As the testes descend through the inguinal canal, portions of the abdominal wall precede them, forming the layers of the scrotal wall and sheath of the spermatic cord.

the same time, the upper gubernacula degenerate. As the testes travel, the layers of the abdominal wall travel ahead, forming the layers of the scrotal wall and spermatic cord (see Figure 9-6). A thin fold of peritoneum, the **processes vaginalis,** also descends, but its connection to the abdomen is lost between the future deep ring of the inguinal canal and the upper pole of the testis. However, it remains in the scrotum as the **tunica vaginalis,** which covers the spermatic cord and testes. In a vast majority of cases, the testes finish their descent and are present in the scrotum at birth.

Internal Genitalia

Around the eighth week after fertilization, Sertoli's cells secrete müllerian-inhibiting substance (MIS), which induces **regression of the paramesonephric (müllerian) duct.** Leydig's cells begin to secrete androgens that stimulate **differentiation of the mesonephric (wolffian) ducts.** The mesonephric ducts form several structures (see Figure 9-7).

- Epididymis: Coiled ducts, form caudally.
- Ductus deferens: Thick smooth muscle coat, ends in prostatic urethra.
- Ejaculatory duct: Located in prostatic urethra.
- Seminal vesicles: At the terminal end.

Another important structure, the **prostate,** forms as an endodermal outgrowth from the urogenital sinus that forms the prostatic urethra. There are two zones of glandular tissue surrounded by mesenchyme. The outer zone of prostatic glands constitutes the **posterior lobe.** The inner zone of mucus glands, which

CLINICAL CORRELATION

Direct inguinal hernias are acquired hernias that occur when bowel protrudes through a weak point of the abdominal wall, the superficial inguinal ring of the inguinal canal. **Indirect inguinal hernias** are congenital hernias and occur when bowel protrudes through a **patent processus vaginalis,** an incomplete closure of the inguinal canal. A **hydrocele** is a collection of serous fluid that can form in the tunica vaginalis.

MNEMONIC

Mesonephric duct derivatives:

Seminal vesicles
Epididymis
Ejaculatory duct
Ductus deferens

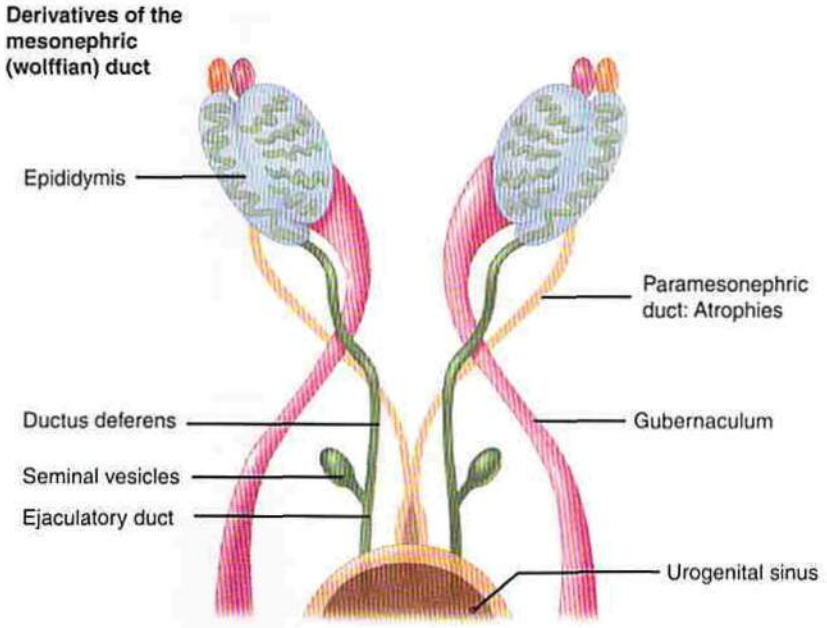


FIGURE 9-7. Male internal genitalia development. The mesonephric (wolffian) duct differentiates to form the epididymis, ductus deferens, seminal vesicles, and ejaculatory duct, while the paramesonephric (müllerian) duct atrophies.

CLINICAL CORRELATION

Adult **prostate cancer** usually occurs in the outer zone of the prostate, while **benign prostatic hyperplasia (BPH)** usually occurs in the inner zone.

constitute the **median lobe**, also contains mesoderm from the mesonepheric duct and müllerian duct remnants.

External Genitalia

Testosterone secreted by Leydig's cells also induces changes in the external genitalia (see Figure 9-8).

- Phallus enlargement becomes the glans (distal end).
- Urogenital fusion ventrally forms the body.
- Labioscrotal fold fusion forms the scrotum.

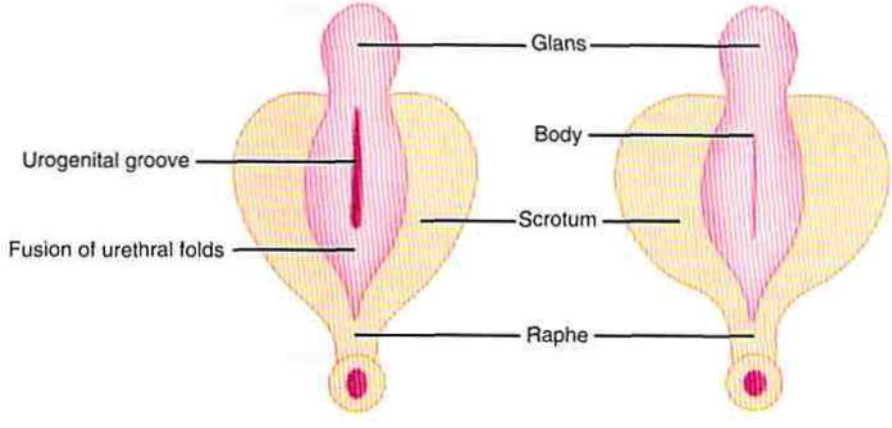


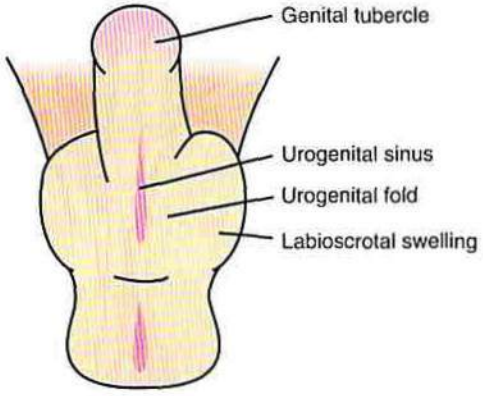
FIGURE 9-8. Male external genitalia development. During development of the male external genitalia the phallus enlarges and the urogenital and labioscrotal folds fuse at the midline. This results in formation of the penile glans, penile body, and scrotum, respectively.

TABLE 9-3. Derivatives of Embryonic Urogenital Structures

	MALE	FEMALE
Mesonephric duct	Ureter, renal pelvic, calyces, collecting tubules, ductus (vas) deferens, duct of epididymis, ejaculatory duct, seminal vesicle.	Ureter, renal pelvic, calyces, collecting tubules.
Paramesonephric duct		Uterus, fallopian tubes.
Urogenital sinus	Urinary bladder, urethra, prostate gland, bulbourethral glands.	Urinary bladder, urethra, vagina, urethral and paraurethral glands, greater vestibular glands.
Gubernaculum	"Scrotal ligament"	Ovarian ligament, round ligament of the uterus.

The urogenital fusion encloses the endodermally-derived urethra. The fusion processes leave a line called the **scrotal and penile raphe**. All structures are covered in ectoderm, but the ectoderm over the glans breaks down to form the **foreskin** or **prepuce**.

Table 9-3 and Figure 9-9 review the internal and external structural homologues between genders.



Male			Female
	Dihydrotestosterone	Estrogen	
Glans penis	←	Genital tubercle	→ Glans clitoris
Corpus spongiosum	←	Urogenital sinus	→ Vestibular bulbs
Bulbourethral glands (of Cowper)	←	Urogenital sinus	→ Greater vestibular glands (of Bartholin)
Prostate gland	←	Urogenital sinus	→ Urethral and paraurethral glands (of Skene)
Ventral shaft of penis (penile urethra)	←	Urogenital folds	→ Labia minora
Scrotum	←	Labioscrotal swelling	→ Labia majora

FIGURE 9-9. Male and female genital homologues.

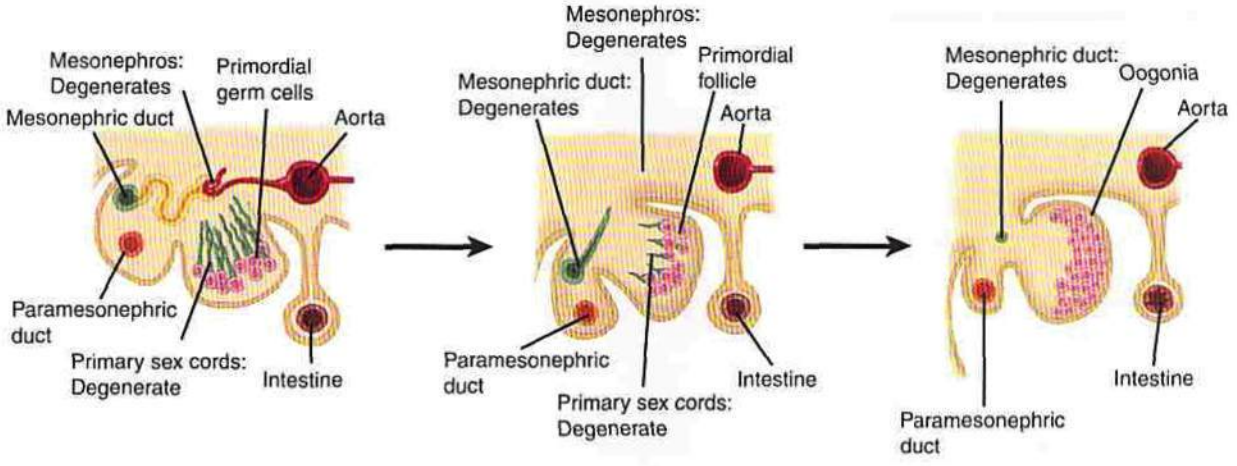


FIGURE 9-10. Ovarian development. As the ovaries develop, the mesonephros and primary sex cords degenerate. The primordial germ cells migrate into the secondary sex cords and form primordial follicles. These follicles then differentiate into oogonia.

Female Development

Ovaries

In the absence of the SRY gene, the indifferent gonads follow a female pattern of differentiation (see Figure 9-10). They differentiate to form:

- Primary sex cords: Degenerate, and secondary sex cords form.
- Secondary sex cords: Break up into **primordial follicles** (a single germ cell + a single layer of mesothelial follicular cells).
- Primordial germ cells: Differentiate to **oogonia,** and undergo mitosis to increase their numbers.
- Mesenchyme: Connective tissue stroma for follicular support.

Before birth, the oogonia enter the first prophase of meiosis and no further division is possible. The ovaries separate from the mesonephros and become suspended in the pelvic mesentery. The peritoneal covering of the ovary is lost. After puberty, the ova are extruded into the peritoneal cavity and gathered into the ostium of the infundibulum by the fimbria.

Internal Genitalia

The female internal genitalia develop due to the **absence of testosterone** and **MIS.** Without these substances, the **mesonephric (wolffian) duct regresses and the paramesonephric (müllerian) duct begins to differentiate.** The paramesonephric ducts partially fuse at the midline to form several structures (see Figure 9-11).

- **Oviduct** (fallopian tubes): Upper, nonfused portion of ducts.
- **Fimbria:** Elongation of oviducts.
- **Uterus:** Lower, fused portion of ducts.
- **Vagina (upper four-fifths):** Lower, fused portion of ducts.

Segments of the oviduct (infundibulum, ampulla, and isthmus) form when muscles and mucous membranes differentiate. The uterus develops a layer of **myometrium** from the surrounding mesenchyme and a layer of peritoneal covering, the **perimetrium** (serosa). The lower fifth of the vagina is formed from two outgrowths from the urogenital sinus wall, the **sinovaginal bulbs.** The ascending sinovaginal bulbs fuse with the descending paramesonephric system, creating the vaginal plate. The vaginal plate canalizes with only the

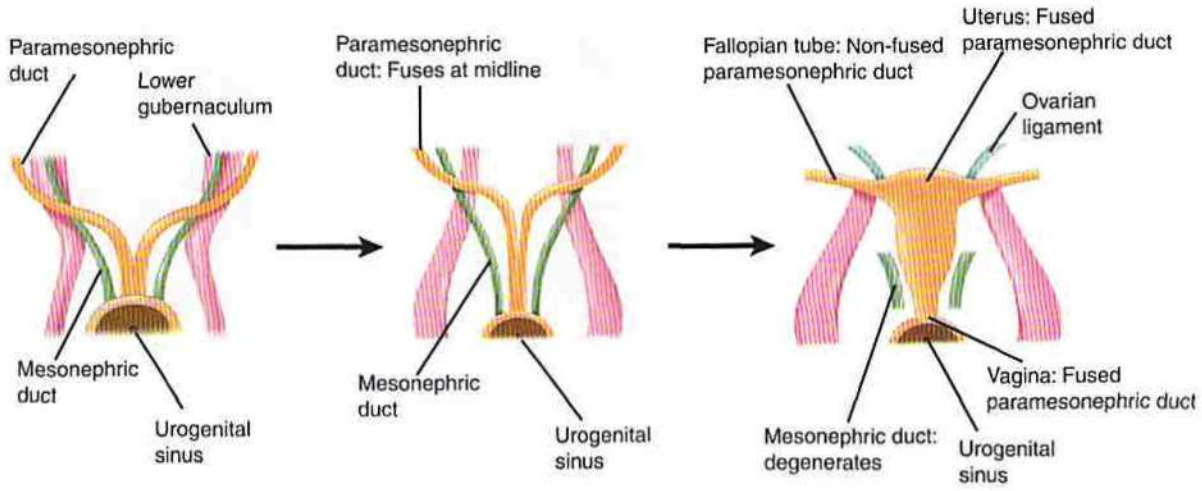


FIGURE 9-11. Female internal genitalia development. The lower portion of the paramesonephric duct fuses at the midline, forming the uterus and upper vagina. The upper portion of the paramesonephric duct does not fuse and forms the oviduct (fallopian tube).

thin covering of the hymen remaining. The greater (**Bartholin's glands**) and the lesser vestibular glands are endodermal outgrowths of the urogenital sinus.

The round ligaments of the ovary and uterus are formed from the gubernaculum attached to the indifferent gonads (see Figure 9-12). The gubernaculum is initially separated into an upper and lower portion. As the müllerian ducts fuse in the midline, the lower ligament is further separated, creating a total of **three segments:** suspensory ovarian ligament, ovarian round ligament, and uterine round ligament.

The **broad ligament,** which covers the entire uterus, develops when the paramesonephric ducts descend through the pelvis, pulling a fold of celomic, or body cavity, epithelium and mesenchyme with them.

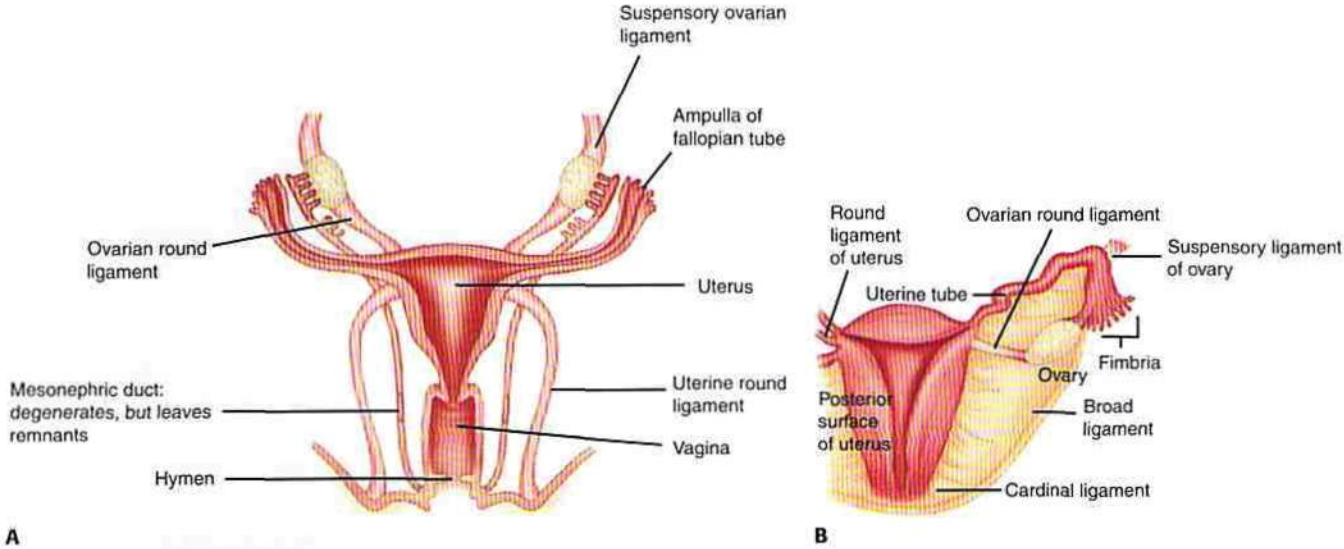


FIGURE 9-12. Female ligament development. The gubernaculum is separated into three segments that form the suspensory ovarian ligament, ovarian round ligament, and uterine round ligament. The broad ligament covers the entire uterus and forms as the developing uterus descends through the pelvis, pulling epithelium and mesenchyme from the lining of the body cavity.

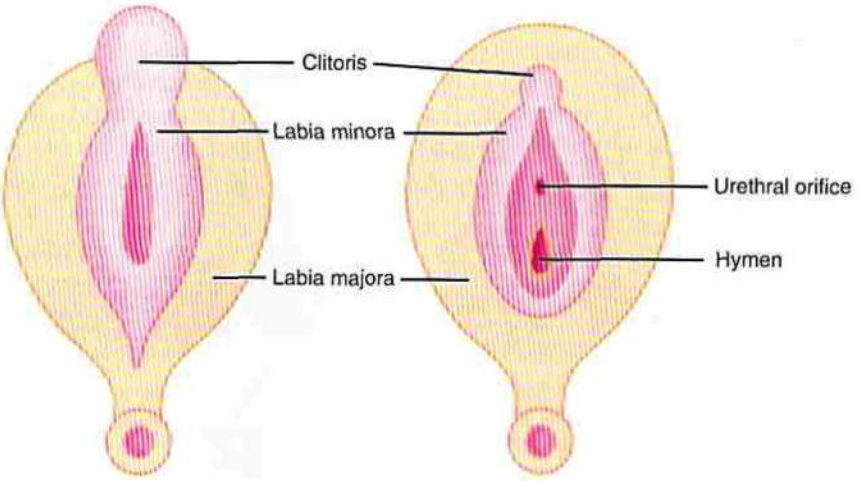


FIGURE 9-13. Female external genitalia development. The genital tubercle develops into the clitoris, while the urogenital and labioscrotal folds develop into the labia minora and labia majora, respectively.

External Genitalia

Under the influence of estrogen (see Figure 9-13):

- Phallus enlarges to become the clitoris.
- Urogenital folds partially fuse to become labia minora.
- Labiosacral folds partially fuse to become labia majora.

The skin covering the clitoris does not break down as in male development, so there is no foreskin equivalent.

Breast Development

Mammary glands develop from apocrine sweat glands in the mesenchymal layer just beneath the skin. Embryologically, breast development is identical in males and females.

- Week 4: The **mammary ridge**, a line of thickened ectoderm, develops from the inguinal region to the axilla.
- Weeks 4–6: The mammary ridge regresses except in the pectoral region.
- Week 6: Single mammary buds form as downgrowths of the mammary ridge.
- Weeks 6–birth:
  - Placental hormones (e.g., lactogen) cause lactiferous duct branching.
  - The surrounding mesenchyme develops into fat and connective tissue.
  - The nipple is formed by depression of the skin before birth.
- Postnatal: The skin surrounding the nipple pit grows, raising the nipple.
- Puberty: If estrogen is present, female mammary glands develop.

CLINICAL CORRELATION

If portions of the mammary ridge do not regress, **accessory nipples** form. This is the most common congenital abnormality of breast development.

Male and Female Genital Homologues

There are several male and female homologues (see Figure 9-9).

CONGENITAL MALFORMATIONS

Gonadal Agenesis

If primordial germ cells do not form or migrate, gonads do not develop and the duct systems and external genitalia differentiate along a female path until birth.

True Hermaphroditism

In true hermaphroditism, which is very rare, there is one ovary, one testis, and external genitalia of both genders.

Pseudohermaphroditism

This condition is characterized by gonads and karyotype of one gender, combined with secondary sex characteristics of the other gender.

- Male pseudohermaphrodites (e.g., testicular feminization)
  - XY, but female phenotype
  - May or may not have testes
- Female pseudohermaphrodites (e.g., adrenogenital syndrome)
  - XX, but male phenotype
  - May or may not have ovaries

CLINICAL CORRELATION

5α-reductase deficiency, one of the more mild forms of male pseudohermaphroditism, leads to deficiency of DHT and thereby to ambiguous external genitalia.

Cryptorchidism

Failure of the testes to descend can occur secondary to abnormalities in either androgen production or shortening of the gubernaculum. Undescended testes typically migrate to the scrotum within 3–6 months of birth. If this does not occur, the child is said to have cryptorchidism and surgical intervention is necessary either to lower them (orchidopexy) or remove them. Undescended testes are unable to produce mature spermatozoa because of the higher temperature inside the body.

CLINICAL CORRELATION

A man with a past history of cryptorchidism has an increased risk of testicular cancer, testicular torsion, inguinal hernia, and subfertility.

Congenital Inguinal Hernia

Incomplete closure of the inguinal canal creates a passage from the abdominal canal to the scrotum through which intestines can herniate.

Hypospadias

This condition is marked by an abnormal opening of the penile urethra on the inferior side of the penis (see Figure 9-14). The opening occurs secondary to failure of the urethral folds to close. If this happens in females, the urethra opens into the vagina. This condition is the most common penile abnormality and must be corrected to prevent urinary tract infections (UTIs).

KEY FACT

Hypospadias occurs more often than epispadias.



FIGURE 9-14. Penile urethral abnormalities. In hypospadias, there is an abnormal opening of the urethra on the inferior side of the penis. In epispadias, there is an abnormal opening of the urethra on the superior side of the penis.

KEY FACT

Hypospadias commonly occurs along with cryptorchidism (10% of boys).

KEY FACT

Exstrophy of the bladder, in which the abdominal wall and bladder are malformed leaving the bladder exposed, commonly occurs with epispadias.

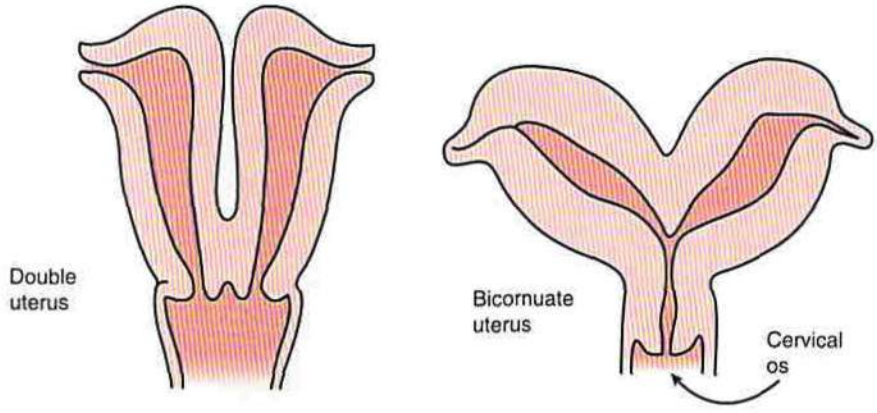


FIGURE 9-15. Uterine canal abnormalities. Abnormal fusion of the paramesonephric ducts results in a double uterus (no fusion) or a bicornuate uterus (incomplete fusion).

MNEMONIC

Hypospadias and epispadias defect locations:

Hypospadias: Urethra opens on the inferior side of the penis (**hypo** = below).

Epispadias: Urethra opens on the superior side of the penis (**epi** = on top of).

Epispadias

This condition is marked by an abnormal opening of the penile urethra on the superior side of the penis. This opening occurs due to malpositioning of the genital tubercle. This condition is associated with exstrophy of the bladder, a condition in which the bladder is exposed, inside out, and protrudes through the abdominal wall.

Uterine Canal Abnormalities

If the paramesonephric ducts fail to fuse at the midline, a double uterus forms. If partial fusion occurs, a bicornuate uterus forms (see Figure 9-15).

Atresia of the Uterine Canal

This condition occurs when there is narrowing or complete occlusion of the paramesonephric ducts (uterine atresia) or of just the sinovaginal bulbs (vaginal atresia).

FLASH BACK

Turner's syndrome can occur due to various anomalies during meiosis or gametogenesis, such as nondisjunction.

Ovarian Hypoplasia

This underdevelopment of the ovary is seen in patients with Turner's syndrome (XO). Primordial germ cells migrate toward the undifferentiated gonad, but follicles do not form. The vulnerable germ cells degenerate and the gonads do not produce hormones after birth, leaving the genitalia in an infantile state.

Anatomy

LOWER ABDOMEN AND PERINEUM

From superficial to deep, the abdominal wall consists of:

- Skin
- Subcutaneous fat
- Scarpa's fascia
- External oblique muscle
- Internal oblique muscle
- Transversus abdominis
- Transversalis fascia
- Preperitoneal fat
- Peritoneum

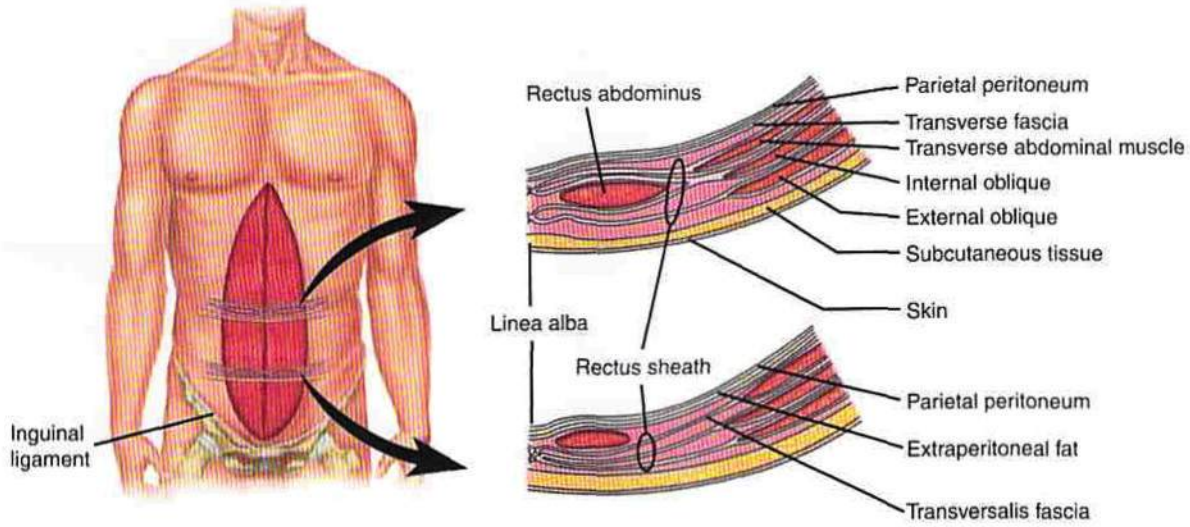


FIGURE 9-16. Layers of the abdominal wall.

The aponeuroses of the abdominal muscles form the rectus sheath. Above the arcuate line, the sheath has anterior and posterior portions that wrap around the rectus abdominis. Below the arcuate line, however, the rectus sheath only travels anterior to the rectus abdominis. In other words, the posterior rectus sheath disappears (see Figure 9-16).

FLASH BACK

Protrusion of peritoneum through the femoral canal results in a femoral hernia.

The inguinal (Poupart's) ligament is derived from the inferior border of the external oblique muscle aponeurosis. This ligament serves as the inferior-lateral border in Hesselbach's triangle, and as the superior-medial border in the femoral triangle (see Figure 9-17).

The pelvic region contains four named fasciae:

- Camper's fascia: Fatty layer of the superficial fascia of the lower abdomen.
- Scarpa's fascia: Membranous layer of the superficial fascia of the lower abdomen (deep to Camper's fascia).
- Buck's fascia: Membranous layer of the deep fascia of the penis.
- Colles' fascia: Membranous layer of the superficial fascia of the urogenital region (perineum).

KEY FACT

Scarpa's and Colles' fasciae are contiguous.

Of these, only Buck's fascia is unique to men.

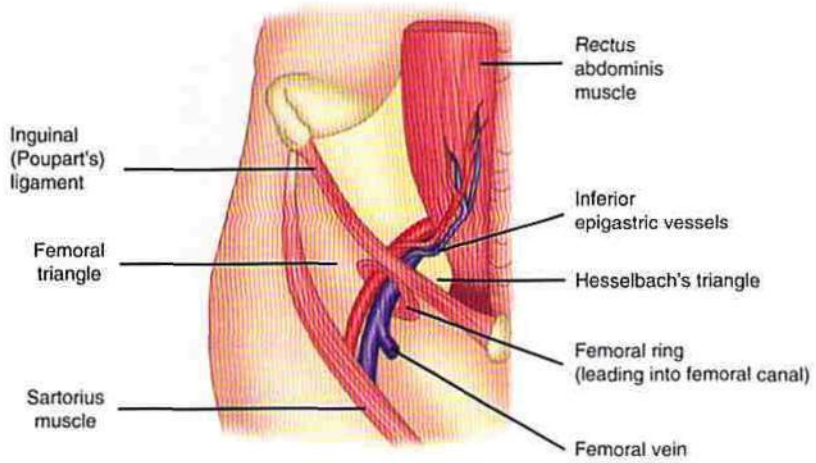


FIGURE 9-17. Anatomic borders formed by the inguinal ligament.

Venous drainage of the gonads differs by side, not gender. Whereas the right gonadal vein drains directly into the **inferior vena cava (IVC)**, the left drains first into the **left renal vein**, which then connects to the IVC.

Lymphatic fluid from the testes and ovaries drains to the para-aortic lymph nodes, regardless of the side of the body.

MNEMONIC

The pathway sperm take to exit the body: **SEVEN UP.**

Seminiferous tubules (site of spermatogenesis)
Epididymis
Vas deferens
Ejaculatory ducts
(**N**othing)
Urethra
Penis

KEY FACT

The superficial vein of the penis is the only subcutaneous penile structure not ensheathed by Buck's fascia.

MALE REPRODUCTIVE SYSTEM

Reproductive structures in the male are located both within and outside the pelvis, as shown in Figure 9-18.

The pelvic fascia are illustrated in Figures 9-19 and 9-20.

The male urethra is composed of three sections: the prostatic urethra (the widest section), the membranous urethra (the section that crosses the urogenital diaphragm and external urethral sphincter), and the spongy urethra (the longest section).

Between the testis and inguinal canal, the vas deferens runs within the **spermatic cord**. Cremasteric muscle fibers, the testicular artery, the pampiniform venous plexus, and the genital branch of the genitofemoral nerve are also found within this structure. The ilioinguinal nerve runs atop the spermatic cord.

In the scrotum, the **tunica dartos**, a thin muscular layer superficial to Colles fascia, allows the scrotal skin to become tense. It also forms the scrotal septum, which keeps the spermatic cords from getting tangled. The **gubernaculum** (sometimes called the "scrotal ligament") further limits movement of the testes by tethering them to the inferior aspect of the scrotum. The left testis often hangs lower than the right.

In conjunction with the **cremaster muscle**, which covers each testis, the tunica dartos allows the testes and scrotum to be drawn up closer to the body in cold environments.

The layers of the scrotum are reviewed in Figure 9-21 and Table 9-4.

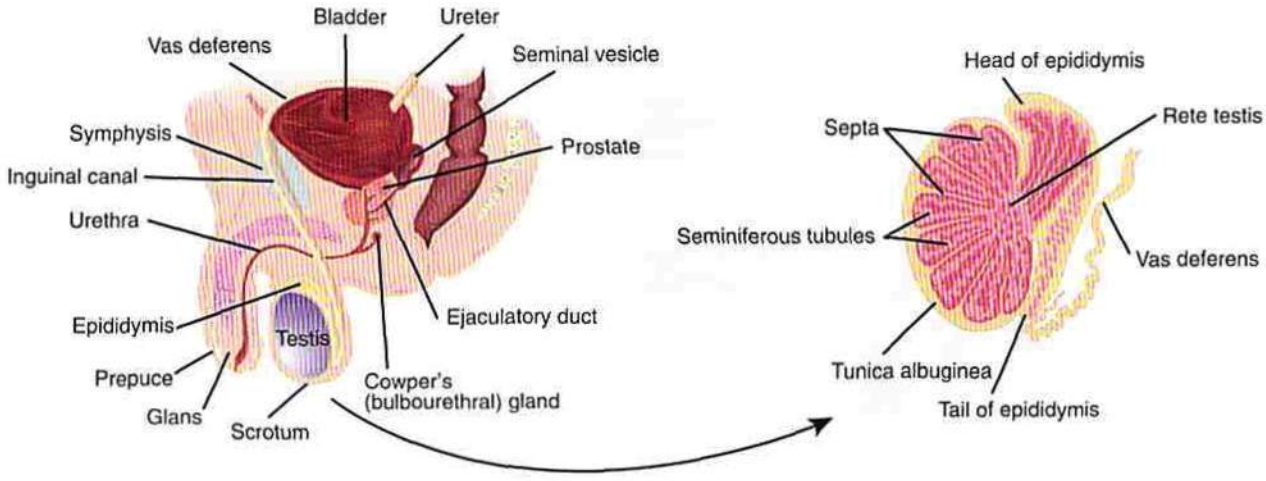


FIGURE 9-18. Lateral view of the male reproductive system.

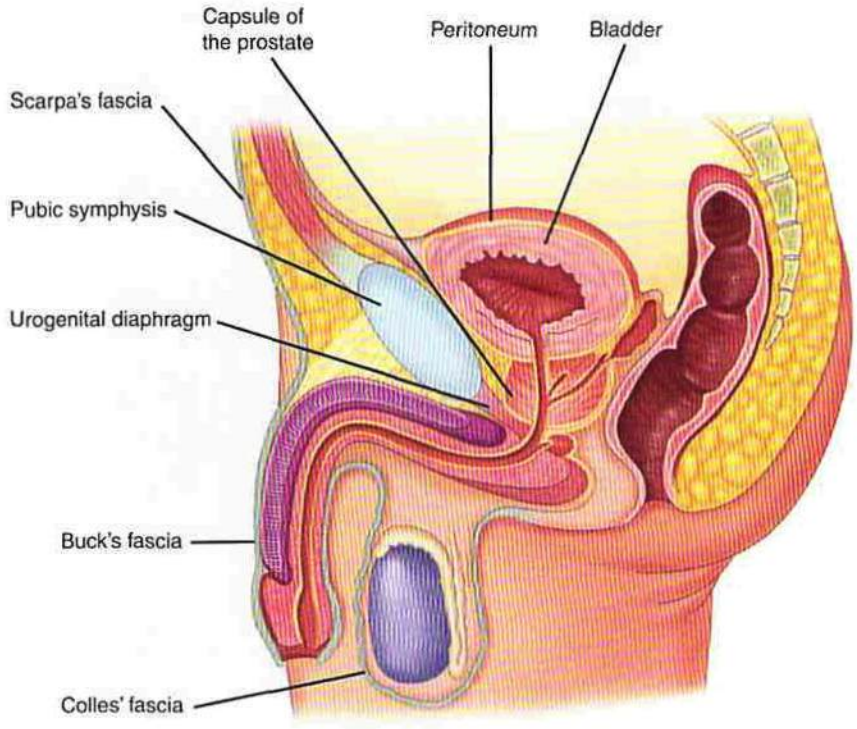


FIGURE 9-19. Lateral view of male perineum.

Sperm Cells

A sperm cell (see Figure 9-22) is composed of a head which includes the nucleus and acrosome, a middle piece, and a tail. The front part of the head contains the **acrosome**, a structure derived from the Golgi apparatus that contains enzymes to digest the extracellular matrix (ECM) and zona pellucida of the egg. The postacrosomal region contains a haploid nucleus. The sperm cell membrane in this region also contains receptors for the egg. The spiral

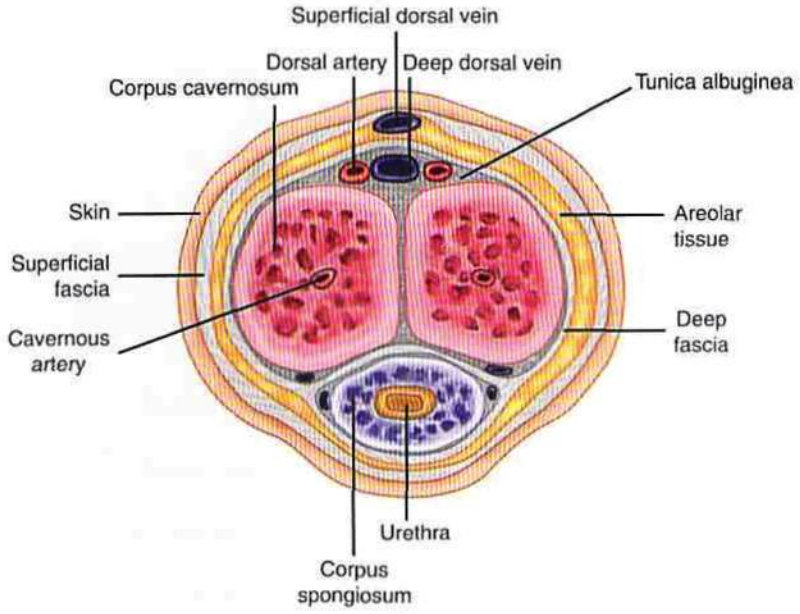


FIGURE 9-20. Cross-section of the penis.

CLINICAL CORRELATION

Testicular torsion involves twisting of the spermatic cord around itself so as to pinch off the blood supply to the testicle. This is a medical emergency; decreased blood flow can result in severe pain and necrosis of the testicular tissue unless blood flow is restored.

CLINICAL CORRELATION

If the processus vaginalis testis (the fetal structure that gives rise to the tunica vaginalis) remains patent, the newborn male baby may develop an **indirect inguinal hernia** into the scrotum.

By contrast, a **direct inguinal hernia**, which does ***not*** enter the scrotum, results from the eventual weakening of the posterior wall of the inguinal canal.

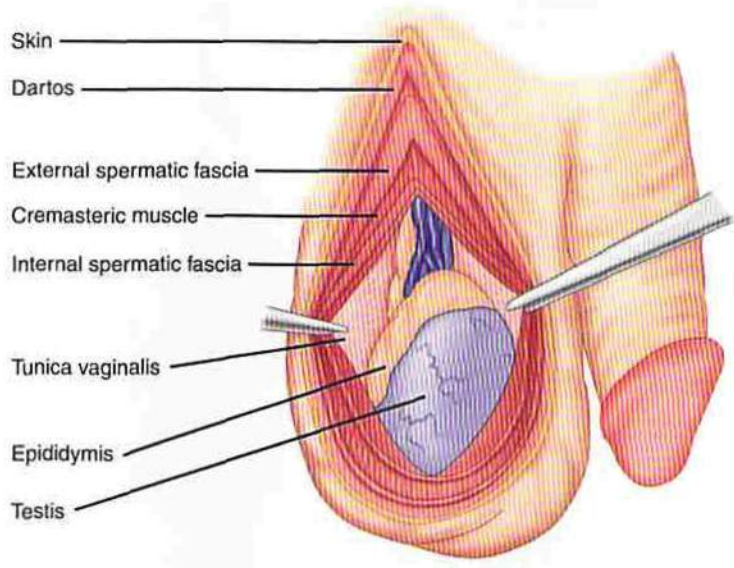


FIGURE 9-21. Layers of tissue within the scrotum. (Modified, with permission, from Brunicardi FC, Andersen DK, Billiar TR, et al. *Schwartz's Principles of Surgery*, 8th ed. New York: McGraw-Hill; 2005: 1522.)

CLINICAL CORRELATION

Mitochondria from the sperm are not included in the conceptus; thus, mitochondria-inherited disorders (eg, Leber's hereditary optic neuropathy and Leigh's syndrome) are passed from the mother.

midpiece consists of fused mitochondria that use fructose to generate adenosine triphosphate (ATP) to move the 9+2 **axoneme** in the proximal portion of the tail. The sliding of the microtubules generates the whip-like motive force characteristic of sperm cells.

Prostate

About the size and shape of a walnut, the prostate stores and secretes a clear, alkaline fluid found in semen. Located at a major anatomic hub with the seminal vesicles and vas deferens, this fluid from the prostate is mixed with seminal fluid and spermatozoa. The ejaculatory ducts, which are located in the middle lobe and lined with transitional epithelium, are found posterior to the urethra. Smooth muscle within the prostate helps expel semen during ejaculation.

KEY FACT

The prostatic tissue itself is strongly controlled by DHT. Normal, age-related increases in estradiol may lead to increased density of DHT receptors and subsequent growth of the prostate (BPH).

Though the gross anatomy of the prostate can described by lobes (see Figure 9-23), the more common approach is by pathologic zones (see Figure 9-24). Table 9-5 lists the approximate equivalencies between the two classification systems.

TABLE 9-4. Spermatic cord derivatives of abdominal layers

Abdominal Structure	Derivative in Spermatic Cord
External oblique muscle aponeurosis	External spermatic fascia
Internal oblique muscle	Cremaster muscle
Transversalis fascia	Internal spermatic fascia
Extraperitoneal fatty tissue	Areolar tissue
Peritoneum	Processus vaginalis

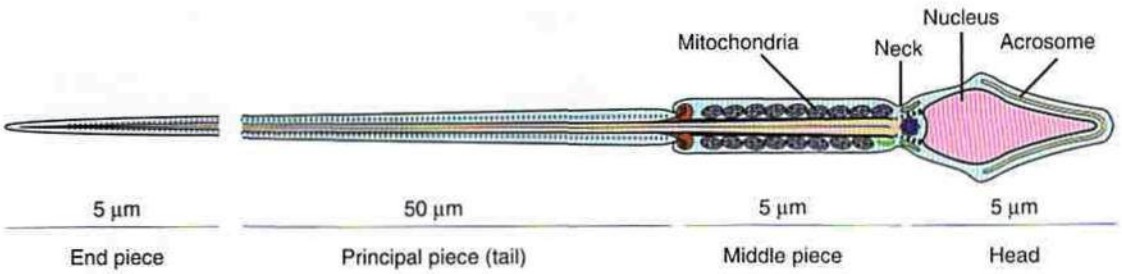


FIGURE 9-22. Sperm anatomy. (Modified, with permission, from Junqueira LC, Carneiro J, *Basic Histology*, 10th ed. New York: McGraw-Hill; 2003.)

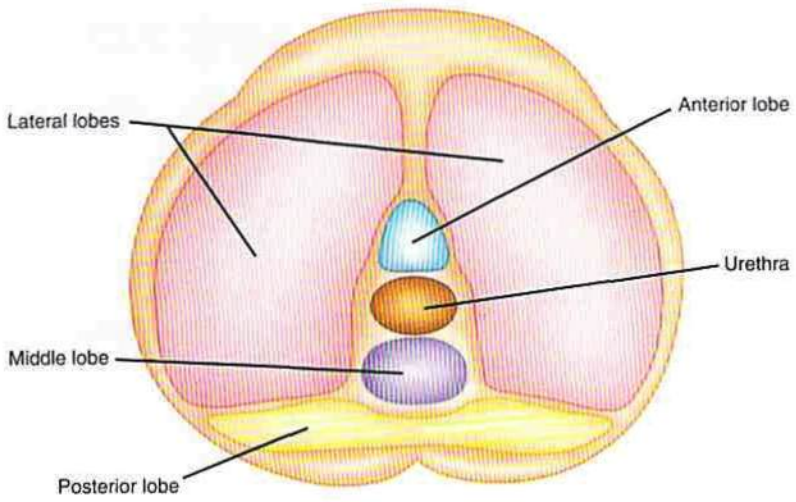


FIGURE 9-23. Prostatic lobes.

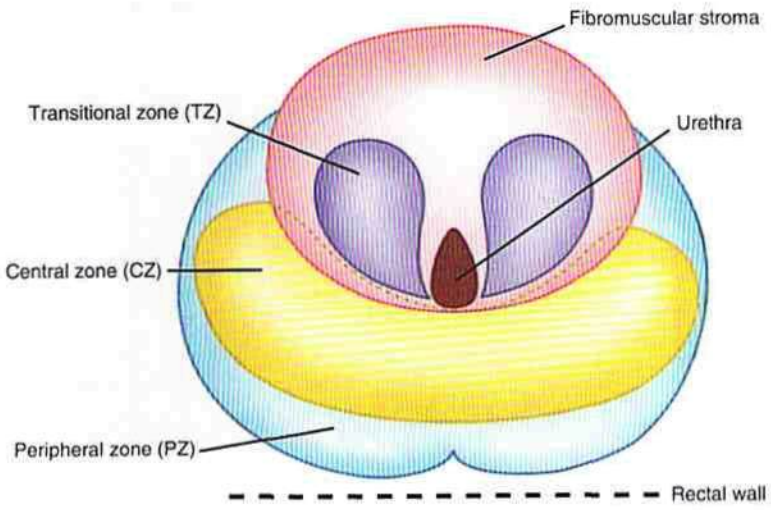


FIGURE 9-24. Prostatic (glandular) zones.

TABLE 9-5. Anatomic Lobes and Pathologic Zones of the Prostate

Anatomic Lobe	Pathologic Zone	Other Structures
Anterior lobe (isthmus)	Transitional zone (TZ)	Proximal urethra
Posterior lobe	Peripheral zone (PZ)	Distal urethra
Middle lobe (median lobe)	Central zone (CZ)	Ejaculatory ducts
Lateral lobe	All zones	

CLINICAL CORRELATION

BPH compresses the estrogen-sensitive cells of the periurethral zone (lateral and middle lobes), resulting in urinary symptoms. **Prostatic adenocarcinoma** affects the androgen-sensitive cells of the peripheral zone, allowing easy metastasis to the spine via Batson's plexus.

FLASH BACK

Remember: The ureters pass under (inferior to) the uterine arteries—"water under the bridge."

The stroma, which accounts for 5% of the weight of the prostate, contains no glands—only muscle and fibrous tissue.

FEMALE REPRODUCTIVE SYSTEM

The female reproductive organs and accessory structures are illustrated in Figure 9-25. In situ, the uterus is usually anteverted (tilted forward), with its antero-inferior face resting against the bladder. As such, it is the posterior side of the uterus that is visualized when looking down at the pelvic floor.

Once released by the ovary, ova are caught by the fimbriae of the fallopian (uterine) tube and travel toward the uterus. The fallopian tubes, also known as the **oviducts** or **salpinges**, contain four sections: the infundibulum, ampulla, isthmus, and interstitium (see Table 9-6).

The ovaries, fallopian tubes, and uterus are held in place by several ligaments (see Figure 9-26):

- **Suspensory ligaments:** Contain the ovarian vessels.
- **Ovarian ligaments:** Run within the broad ligaments and attach the ovaries to the uterus.
- **Round ligaments:** Do not contain any important structures, but help maintain anteversion of the uterus.

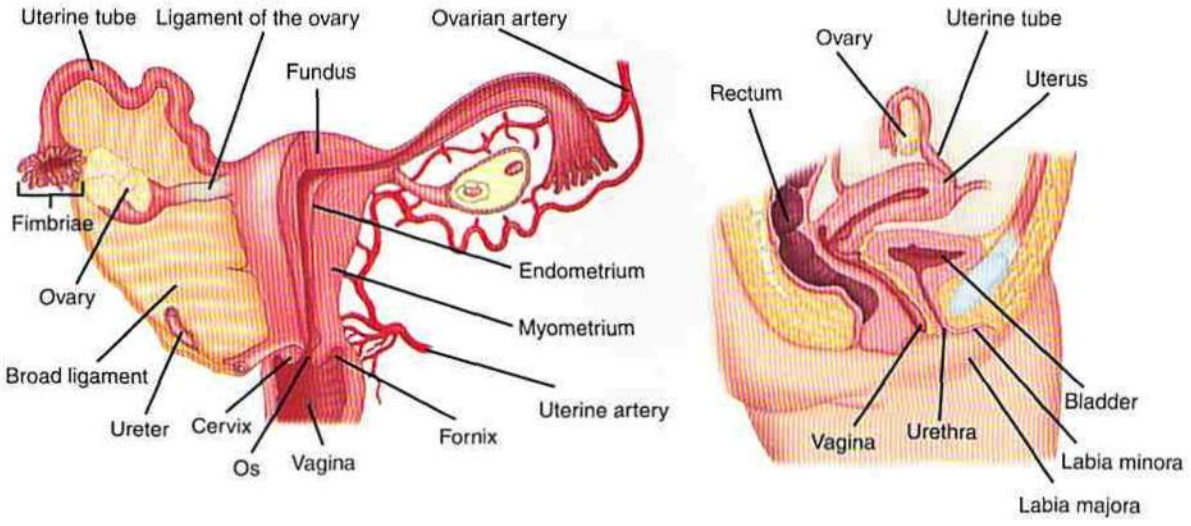


FIGURE 9-25. Posterior and lateral views of female reproductive system. In the left image, the ureter runs perpendicular to the plane of the page (the broad ligament).

TABLE 9-6. Segments of the Fallopian Tubes

SEGMENT	FEATURES	CROSS-SECTION
Infundibulum	Contains fimbriae.	Widest in diameter.
Ampulla	Usual site of fertilization.	Elaborate folds of mucosa with a thin muscularis externa and serosa.
Isthmus		Narrowest diameter; less mucosa and more muscle and serosa than the ampulla.
Interstitium	Connects to the inside wall of the uterus.	Similar in overall diameter to the ampulla, but with a small mucosal opening and very thick muscularis externa.

- **Broad ligament:** Contains the round ligaments of the uterus, the fallopian tubes, the ovaries, and the ovarian ligaments.
- **Transverse cervical (cardinal) ligaments:** Contain the uterine vessels.
- **Uterosacral ligaments:** Connect the uterine cervix to the sacrum, helping to support the uterus and keep it in place.

The pelvic fascia are labeled in Figure 9-27. As in the male, the female urogenital diaphragm is bordered by superior and inferior fascia. Colles fascia is continuous with the posterior aspect of the inferior fascia.

Ova

The female sex cell, the ovum, is a spherical structure produced within **graafian follicles** in the ovary. The outermost layer, the **corona radiata**, is two to three cells thick and is derived from the granulosa cells on the inner portion of the ovarian follicle. Deep to the corona radiata is the **zona pellucida (striata)**, a glycoprotein layer that binds to invading sperm cells and allows the acrosome reaction to occur. Deeper still is the **perivitelline space**, which contains both the mature oocyte and, after fertilization, the second polar body. The mature oocyte possesses a cell membrane, copious cytoplasm, and a haploid nucleus.

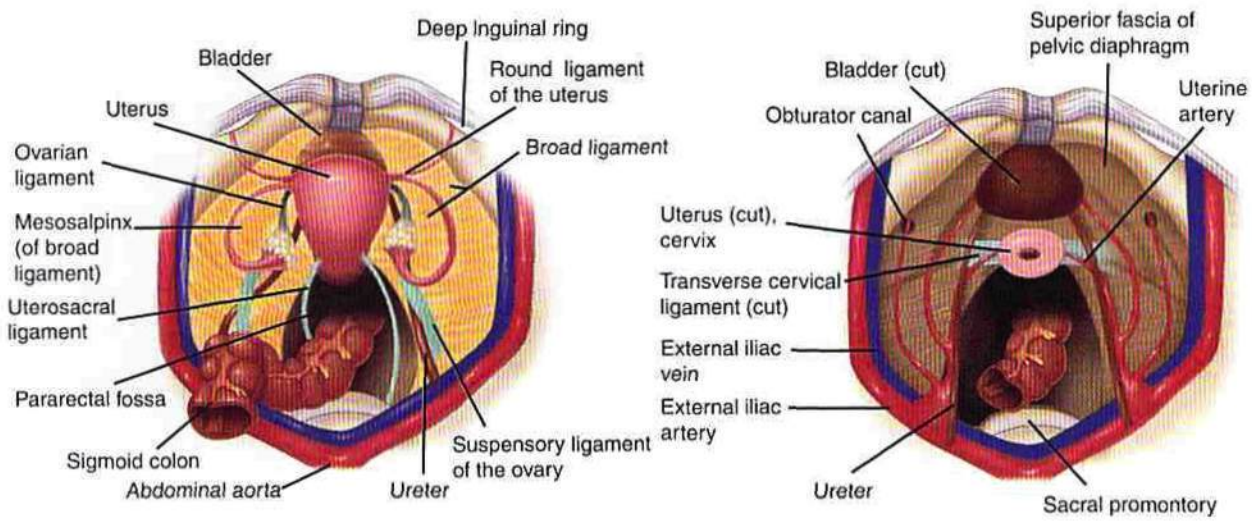


FIGURE 9-26. Superior view of the ligaments of the uterus and ovaries in situ. The right image, with the peritoneum and uterus removed, more clearly shows the course of the ureter, uterine vessels, and transverse cervical ligaments.

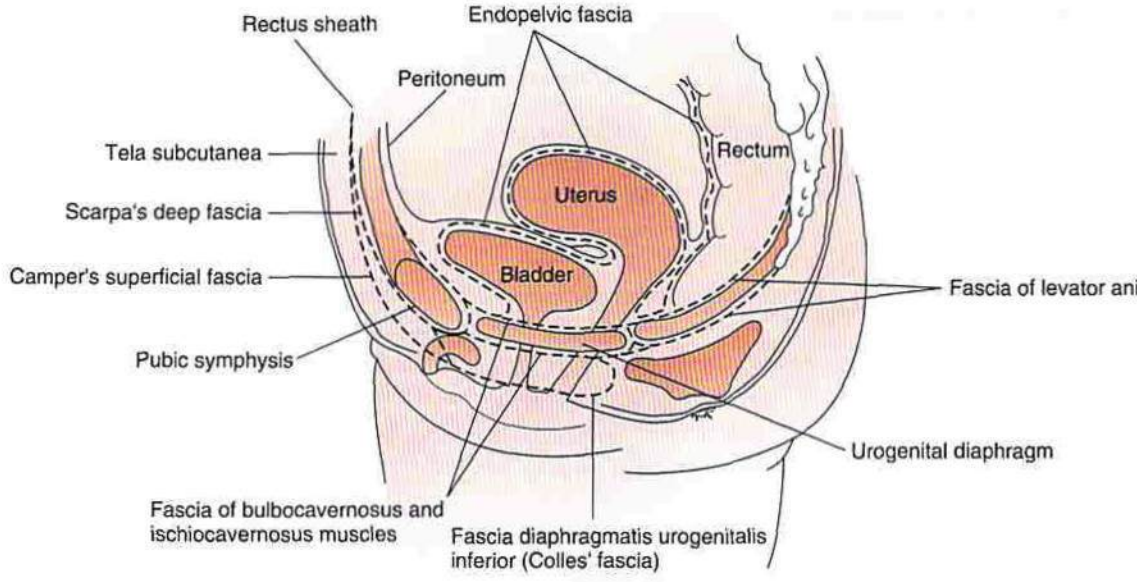


FIGURE 9-27. Lateral view of the female perineum. (Modified, with permission, from Benson RC: *Handbook of Obstetrics & Gynecology*, 8th ed. South Norwalk, CT: Appleton & Lange, 1983. © The McGraw-Hill Companies.)

KEY FACT

Sir Astley Paston Cooper has several ligamentous eponyms. Whereas Cooper's ligament**s** (plural) refer to those in the breast, Cooper's ligament (singular) can indicate either the pectineal ligament in the inguinal region or the transverse ligament of the elbow.

The Breasts

Breast tissue, a composite of connective tissue (collagen and elastin), adipose tissue, and glands, changes over time and secondary to hormonal influences. At puberty, the breasts increase in size and softness as the mammary glands develop and more fat is deposited. After the birth of a child, the number of glands roughly doubles, allowing for the secretion of milk. Overproduction of estrogen, either during menstruation or at the beginning of menopause, can make the breast tissue more tender. The consistency of the breast tissue itself also varies during this period. With time, **Cooper's ligaments**, or the suspensory ligaments of the breast, weaken.

A normal breast (see Figure 9-28) possesses a nipple surrounded by the **areola**, a pigmented section of skin containing sebaceous glands. The mammary

KEY FACT

Lymph node involvement is an intermediate step between local and widespread breast carcinoma. This is why sentinel lymph node biopsies are important in evaluating TNM staging.

CLINICAL CORRELATION

Breast cancer in situ: Ductal carcinoma in situ (DCIS) tends to occur ipsilaterally, whereas lobular carcinoma in situ (LCIS) has a greater chance of affecting both breasts.

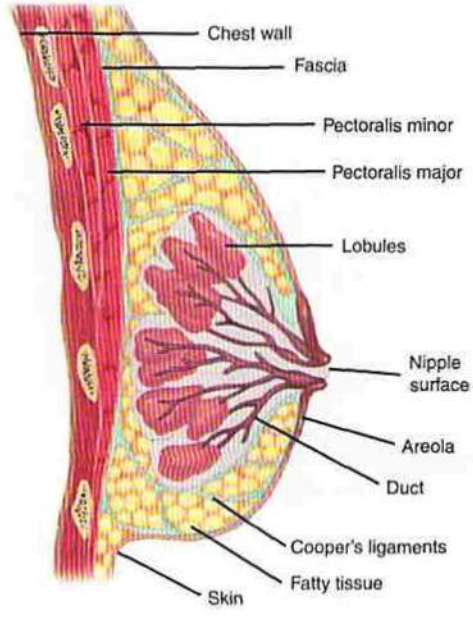


FIGURE 9-28. Lateral view of the female breast.

TABLE 9-7. Principal Nerves and Vessels of the Breast

Nerves	Anterior and lateral cutaneous branches of thoracic intercostal nerves T3–T5.
Arteries	Internal thoracic (internal mammary) artery, lateral thoracic artery, thoracodorsal artery, thoracoacromial artery.
Veins	Axillary vein, internal thoracic vein, intercostal vein.

glands within the breast tissue connect to the nipple via lactiferous ducts. The breast itself sits atop the pectoralis major muscle, spanning from approximately the second to the sixth rib, though a thin layer of mammary tissue reaches several ribs above and below. The "tail of Spence" extends diagonally from the superior lateral quadrant to the axilla.

The majority of the lymph from the breast drains to the ipsilateral axillary lymph nodes. The parasternal, abdominal, and contralateral axillary lymph nodes may also be involved.

The nipples in both men and women are highly sensitive and highly vascular. Table 9-7 and Figure 9-29 review the important nerves and vessels in the breast.

KEY FACT

The dermatome at the level of the nipple is T4.

FLASH BACK

Ploidy = number of homologous sets of chromosomes (i.e., diploid indicates input from both parents, whereas haploid indicates *contribution by only one*).

Chromatid = one-half of a replicated chromosome.

Physiology

GAMETOGENESIS

Human sexual reproduction is dependent on many factors, but formation of healthy gametes is probably the most important. Though the synchronicity and location of spermatogenesis and oogenesis differ, the cells go through nearly analogous stages (as suggested by their suffixes). Table 9-8 reviews these stages.

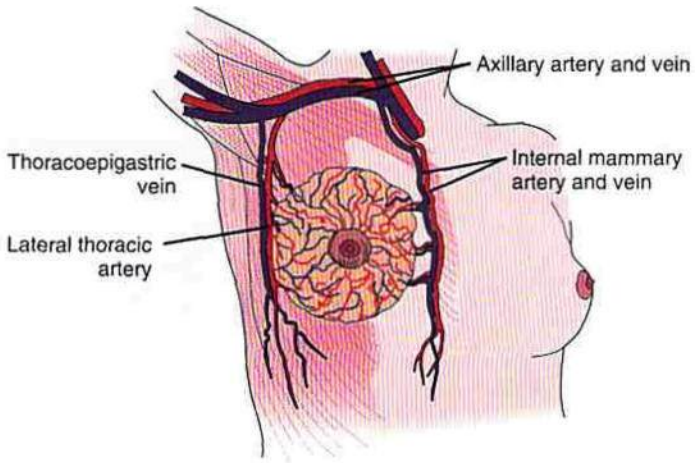


FIGURE 9-29. Selected vessels in the female breast. (Modified, with permission, from DeCherney AH, Nathan L, *Current Obstetric & Gynecologic Diagnosis & Treatment*, 10th ed, New York: McGraw-Hill; 2007: 1033.)

TABLE 9-8. Overview of Gametogenesis in Males and Females

Chromosomes	Cell Type (Singular Form)	Chromatids
Diploid (46)	Spermatogonium/oogonium	2N
	Primary spermatocyte/primary oocyte	4N
Haploid (23)	Secondary spermatocyte/secondary oocyte	2N
	Spermatid/ootid	N
	Spermatozoon/ovum	

SPERMATOGENESIS

Spermatogenesis, which occurs in the seminiferous tubules of the testes, is a simple stepwise process of mitosis and two rounds of meiosis (see Figure 9-30). It is important to note two things: (i) Some spermatogonia undergo mitosis (replication) but do not advance further, thus maintaining a constant supply of cells for spermatogenesis, and (ii) dividing sperm cells remain connected by threads of cytoplasm so they develop at the same time (see Figure 9-31). Upon release from Sertoli's cells, mature but nonmotile spermatozoa move from the lumen of the seminiferous tubules to the epididymis where they become motile. However, it is muscle contraction in the male reproductive tract rather than flagellar movement that moves the sperm cells prior to ejaculation.

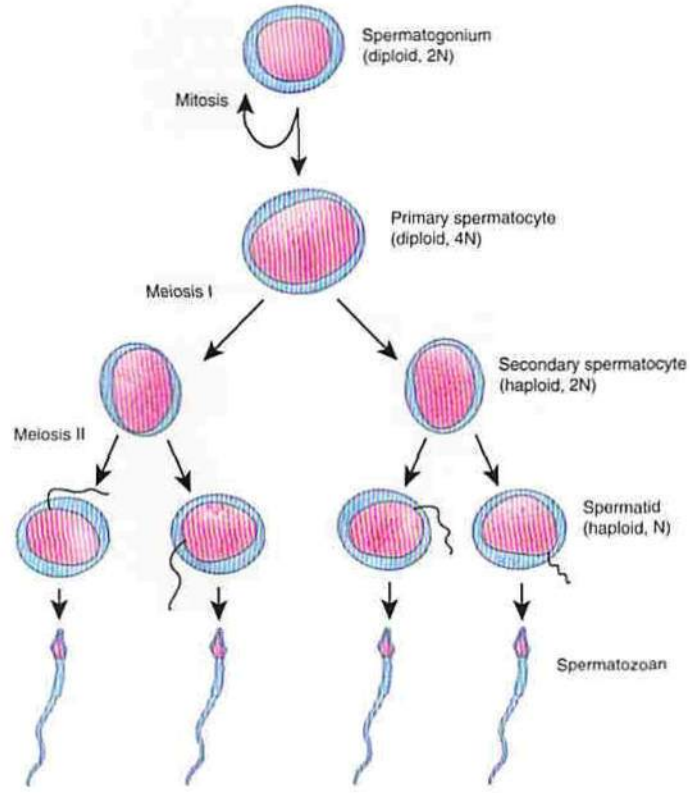


FIGURE 9-30. Spermatogenesis.

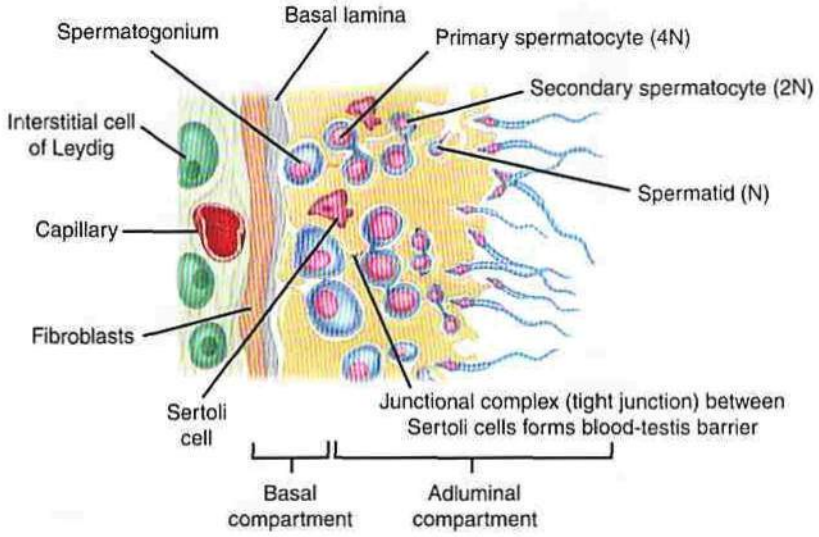


FIGURE 9-31. Cells of the seminiferous tubules.

Sertoli's cells make numerous contributions to developing sperm cells, including:

- The **blood-testis barrier**, which blocks penetration by cytotoxic agents.
- Secretion of substances that aid in meiosis.
- Phagocytosis of residual cytoplasm left over following spermiogenesis.
- Secretion of other factors, including androgen-binding protein (ABP), inhibin, giant cell line–derived neutrophilic factor (GDNF), and estradiol.

Leydig's cells can also produce estradiol, although they mainly produce testosterone.

The effects of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) on Sertoli's and Leydig's cells are illustrated in Figure 9-32.

Spermatogenesis begins at puberty and continues until death, although the quantity and quality of the sperm cells wane somewhat in the later years as plasma testosterone levels fall.

OOGENESIS

Oogenesis occurs in the ovarian follicle of the ovary without the aid of centrosomes. It is analogous to spermatogenesis, although the timing is different:

- Oocytogenesis is completed in the perinatal period, thus providing a newborn female with all the oocytes she will ever have ($\sim 7 \times 10^6$).
- Primary oocytes are arrested in prophase I until ovulation. This period is called **dictyate** or **dictyotene**.
- Secondary oocytes are arrested in metaphase II until fertilization.
- The ootid cell type appears within minutes of fertilization and quickly becomes an ovum before parental and maternal pronuclei combine and a zygote is formed.

Also in contrast to spermatogenesis, the effort in oogenesis is concentrated on one cell. The two **polar bodies** degenerate (see Figure 9-33).

Until ovulation (and possible subsequent fertilization) occurs, maturation of the oocyte takes place within an ovarian follicle (see Figure 9-34).

KEY FACT

Sertoli's cells are supporting nurse cells.
Leydig's cells are steroidogenic interstitial cells.

FLASH BACK

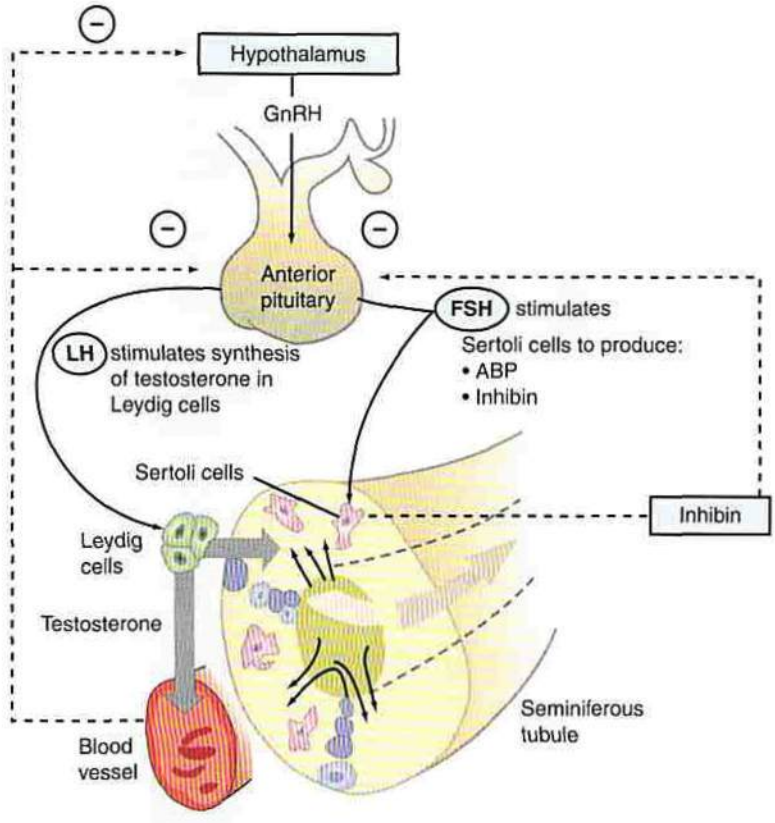
Steroid hormones are not stored in cells; their level in the bloodstream is dependent on their rate of synthesis.

CLINICAL CORRELATION

Recent research has suggested that germline stem cells may help renew ovarian follicles, a claim that challenges the current dogma that a finite number of oocytes exist at birth.

KEY FACT

Upon fertilization, meiosis II is completed, allowing the secondary oocyte to become a **haploid** ootid/ovum and avoiding multiploidy.



PRODUCTS	FUNCTIONS OF PRODUCTION
Androgen-binding protein (ABP)	Ensures that testosterone in seminiferous tubule is high.
Inhibin	Inhibits FSH.
Testosterone	Differentiates male genitalia, has anabolic effects on protein metabolism, maintains gametogenesis, maintains libido, inhibits GnRH, and fuses epiphyseal plates in bone.

FSH → Sertoli cells → Sperm production

LH → Leydig cells → Testosterone

FIGURE 9-32. Hormonal regulation of spermatogenesis. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.

FLASH BACK

Breast budding **(thelarche)** and growth of pubic hair are the first signs of a girl's entry into puberty. Physicians monitor these changes using Tanner staging.

KEY FACT

Form follows function: Granulosa cells line the interior of the follicle, and theca cells form the outer border.

MENSTRUAL CYCLE AND OVULATION

Menarche, or a woman's first menstrual period, occurs, on average, at 12.5 years of age in American girls. It precedes regular ovulation from several months to up to a year. Figure 9-35 illustrates the timing of this and other pubertal events.

Granulosa cells, the female analogue of Sertoli's cells, also respond to FSH and encourage growth of 15–20 follicles. LH-responsive theca cells stimulate growth of the corpus luteum and produce androgens, which can be converted to estrogen by the granulosa cells.

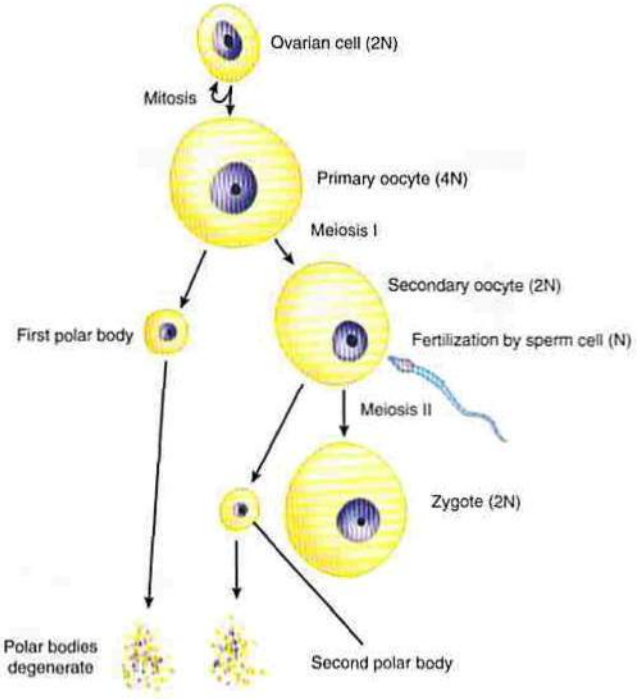


FIGURE 9-33. Oogenesis and fertilization.

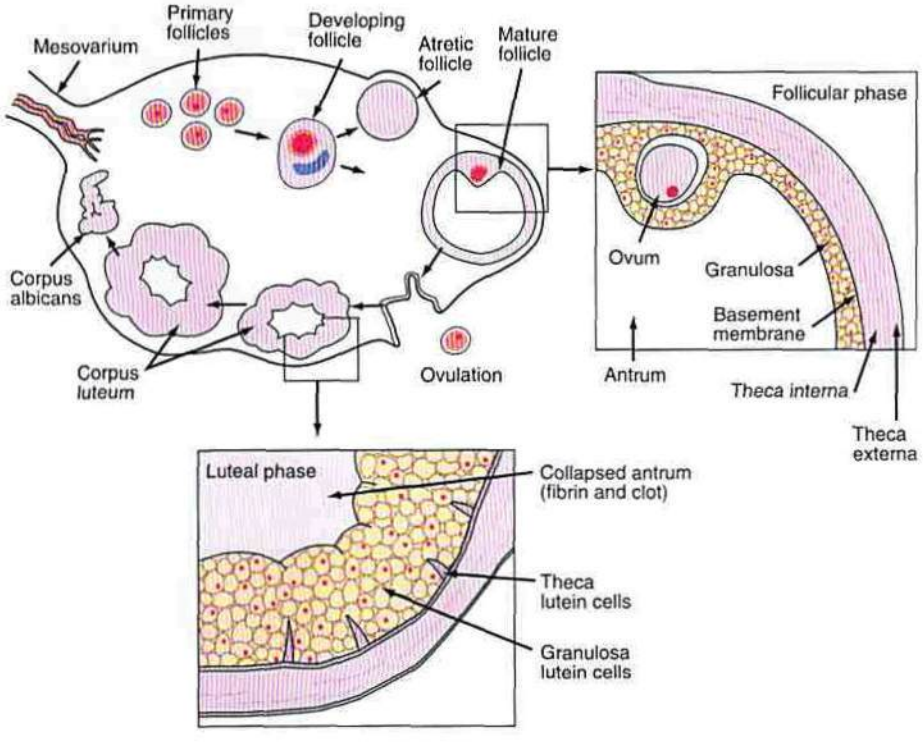


FIGURE 9-34. Follicular development in situ. (Reproduced, with permission, from Kasper DL, Braunwald E, Fauci AS, et al, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill; 2005: 2199.)

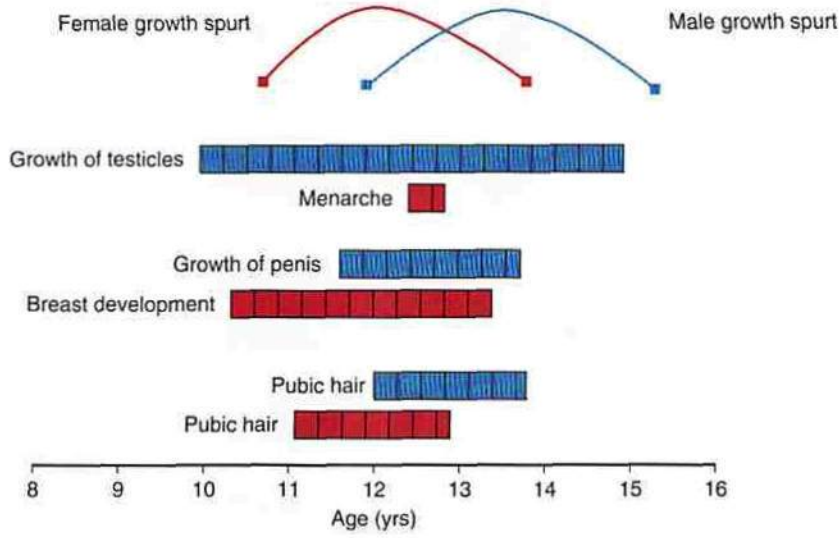


FIGURE 9-35. Comparison of pubertal events in an average American boy and girl.

KEY FACT

In the follicular phase, estrogen provides positive feedback to the hypothalamus and anterior pituitary. In the luteal phase, estrogen and progesterone inhibit gonadotropin secretion.

KEY FACT

A rise in progesterone level indicates recent ovulation.

MNEMONIC

Progesterone **p**repares for and maintains **p**regnancy.

Estrogen encourages growth of the endometrium and provides positive feedback to the anterior pituitary to stimulate the release of more FSH and LH (see Figure 9-36), leading to the midcycle **gonadotropin surge**. (Androgens, however, inhibit GnRH and gonadotropin secretion by negative feedback.)

Approximately 1 week before ovulation, one of the developing follicles becomes dominant, or more sensitive to FSH. This follicle secretes inhibin, blocking the production of FSH from the anterior pituitary and thus causing the other follicles to undergo atresia. In anticipation of a pre-ovulatory rise in estrogen levels from the FSH-independent dominant follicle, granulosa cells express both FSH and LH receptors, and theca cells increase their expression of LH receptors. An LH surge results in ovulation.

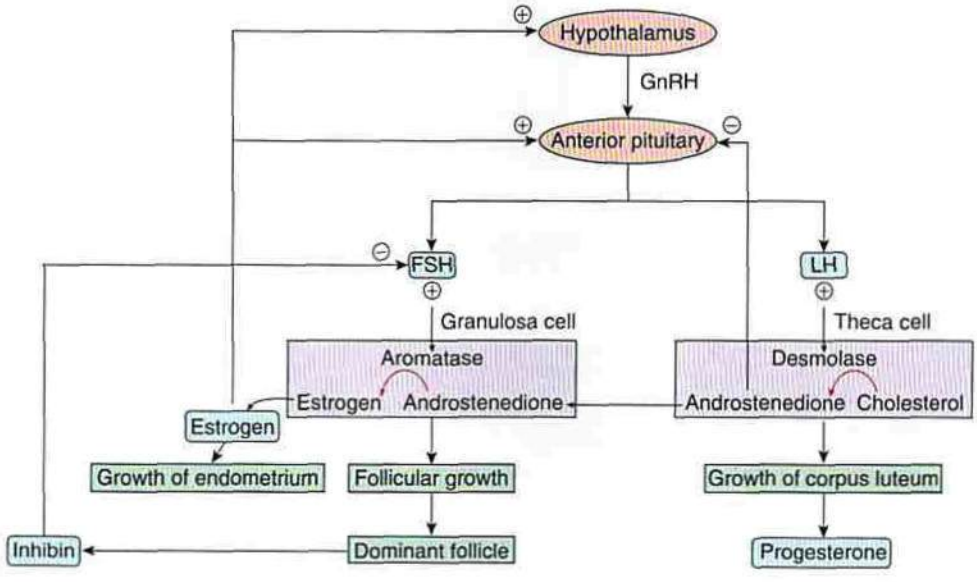


FIGURE 9-36. Female hormonal axis (follicular phase). FSH = follicle-stimulating hormone; GnRh = gonadotropin-releasing hormone; LH = luetinizing hormone.

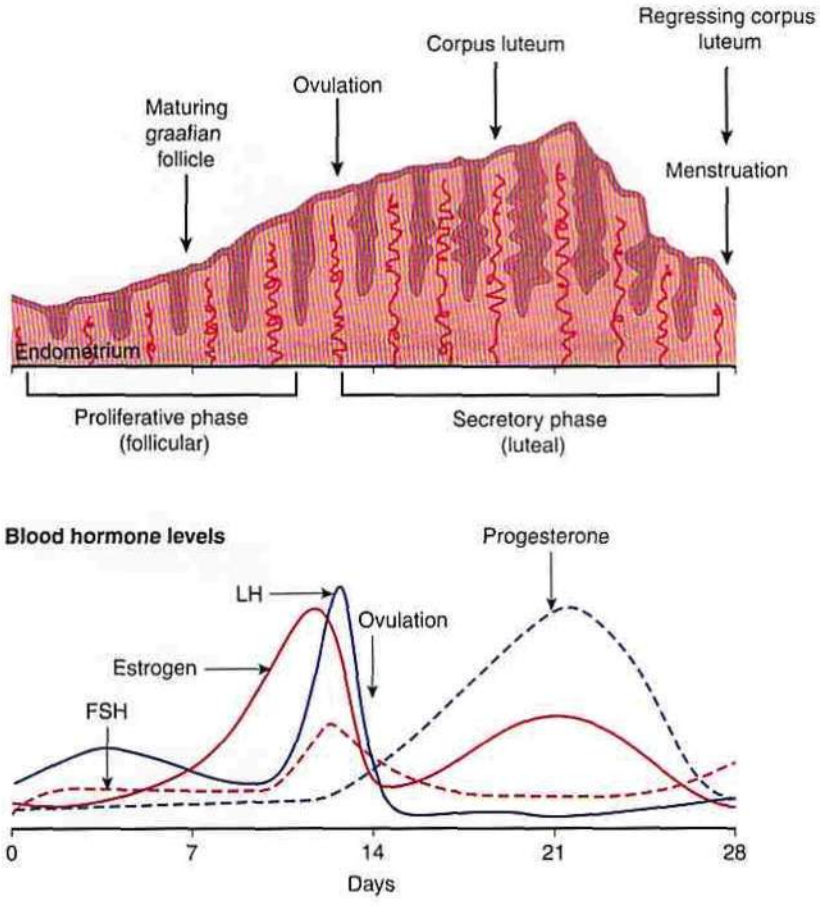


FIGURE 9-37. Endometrial and hormonal changes in a menstrual cycle. FSH = follicle-stimulating hormone; LH = luteinizing hormone.

If fertilization occurs, the extra-embryonic trophoblasts produce **human chorionic gonadotropin (hCG)**. This hormone acts like LH and causes the corpus luteum to secrete progesterone, stimulating further growth of the endometrium.

If fertilization does not occur (see Figure 9-37), the corpus luteum soon degenerates into a mass of scar tissue called the **corpus albicans**. Consequently, estrogen and progesterone levels drop, and the functional portion of the endometrium is shed via menstruation. The whole process of follicular recruitment through menstruation takes approximately 28 days.

Figure 9-38 shows the variation of FSH and LH levels with age. These two hormones normally stimulate production of estrogen, but after menopause, estrogen levels drop, despite continuing high levels of FSH and LH. A woman's lifetime estrogen exposure is an important risk factor for the development of breast cancer. Increased estrogen exposure is associated with early menarche, late menopause, nulliparity, and not breast-feeding.

CLINICAL CORRELATION

hCG is used to detect pregnancy because it appears in the urine 8 days after successful fertilization.

CLINICAL CORRELATION

Insulin stimulates the ovaries to produce estrogen. Consequently, diabetics may have a greater risk of breast cancer and endometrial carcinoma.

FLASH BACK

A female fetus has high levels of FSH and LH during the second trimester, owing to development of the genitalia.

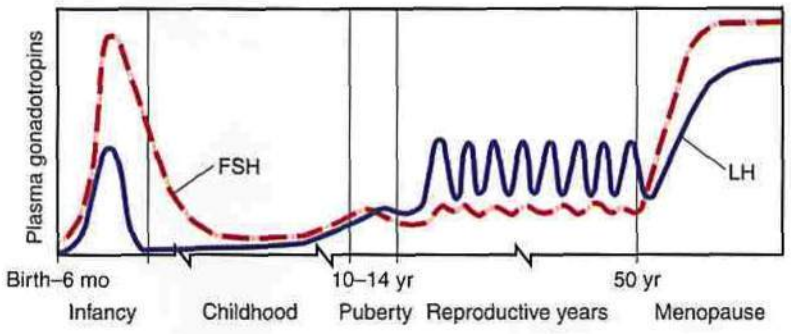


FIGURE 9-38. Plasma gonadotropin levels throughout a woman's lifetime. FSH = follicle-stimulating hormone; LH = luteinizing hormone. (Modified, with permission, from Kasper DL, Braunwald E, Fauci AS, et al, *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill; 2005.)

KEY FACT

The zona fasciculata and zona reticularis work together. Since the zona reticularis is not fully functional for several years after birth, the zona fasciculata ends up working harder, becoming the thickest layer in the adrenal cortex.

GONADAL STEROIDS

Steroid hormones, which are derived from cholesterol (see Figure 9-39), can be organized into five groups: mineralocorticoids, glucocorticoids, androgens, estrogens, and progestagens. The latter three groups are vital for normal genital development, and later, fertility. Their functions are reviewed in Table 9-9. Dehydroepiandrosterone (DHEA), a weak androgen, and androstenedione are both produced in the adrenal gland (zona reticularis) and the gonads. By comparison, the stronger androgens and estrogens (e.g., DHT and estradiol) are primarily produced in the gonads.

KEY FACT

Testosterone and androstenedione are converted to estrogen in adipose tissue by the enzyme **aromatase**.

? CLINICAL CORRELATION

Like hyperinsulinemia, obesity can increase the risk of breast cancer. Adipocytes allow peripheral conversion of androstenedione to estrogen.

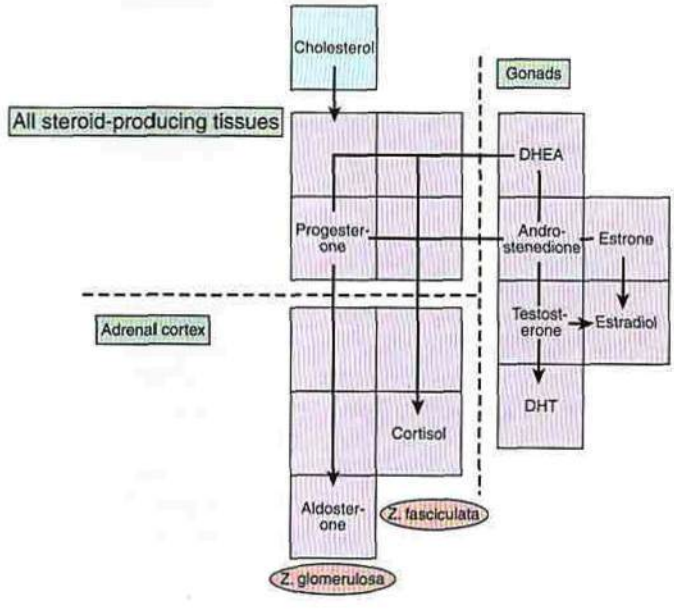


FIGURE 9-39. Organization of steroid hormone synthesis. Dihydrotestosterone (DHT) is produced by peripheral conversion. Estradiol can be made directly in the gonads or by peripheral conversion as well.

TABLE 9-9. Androgens, Estrogens, and Progestagens

ANDROGENS	
Source	Testis (DHT and testosterone), adrenal glands (androstenedione).
Biological potency	DHT > testosterone > androstenedione.
Targets	Skin, prostate, seminal vesicles, epididymis, liver, muscle, brain.
Function	1. Differentiation of the wolffian duct system into internal gonadal structures. 2. Secondary sexual characteristics and growth spurt during puberty. 3. Required for normal spermatogenesis. 4. Anabolic effects (increased muscle size, increased RBC production). 5. Increased libido.
ESTROGENS	
Source	Ovary (estradiol), placenta (estriol), adipose (aromatization).
Biological potency	Estradiol > estrone > estriol.
Function	1. Growth of follicles. 2. Endometrial proliferation. 3. Development of genitalia. 4. Stromal development of the breast. 5. Female fat distribution. 6. Hepatic synthesis of carrier proteins. 7. Feedback inhibition of FSH. 8. LH surge (estrogen feedback on LH and FSH secretion switches from negative to positive just before the LH surge). 9. Increased myometrial excitability. 10. Increased HDL, decreased LDL.
PROGESTAGENS	
Source	Corpus luteum, placenta.
Function	1. Stimulation of endometrial glandular secretions and spiral artery development. 2. Uterine smooth muscle relaxation. 3. Decreased myometrial excitability. 4. Maintenance of pregnancy. 5. Production of thick cervical mucus, which inhibits sperm entry into the uterus. 6. Increased body temperature. 7. Positive and negative regulation of gonadotropins (LH, FSH).

KEY FACT

Progesterone is the only naturally-occurring human progestagen. Progestins are synthetic progestagens used for hormonal contraception.

MNEMONIC

PRiSM: **P**rogestagens cause **R**elaxation of **S**mooth **M**uscle, which accounts for vasodilation and decreased myometrial excitability and GI motility.

KEY FACT

The parasympathetics stimulate the release of nitric oxide (NO), which, via cyclic guanosine monophosphate (cGMP) in vascular smooth muscle, closes Ca^{2+} channels. The arterial smooth muscle relaxes, and the erectile tissue fills with blood.

CLINICAL CORRELATION

Sildenafil, a pharmacologic agent used to treat erectile dysfunction, acts by competitively inhibiting phosphodiesterase 5 (PDE5), an enzyme that degrades cGMP.

MNEMONIC

Point and **S**hoot

Parasympathetic
Sympathetic

SEXUAL RESPONSE

The trajectory of sexual interaction in both men and women consists of four phases: desire, excitation, orgasm, and resolution. Men experience increased blood flow into and decreased venous return out of the cavernous spaces of the penis, yielding an **erection**. Women, too, experience similar changes in blood flow to the clitoris and vestibular bulbs. This is all mediated by the pelvic splanchnic nerves (parasympathetics, S2–S4).

In men, orgasm consists of two sub-steps: **seminal emission** and **antegrade ejaculation**. The sympathetic nervous system (T10–L2) controls closure of the bladder neck, contraction of the seminal vesicle, and deposition of semen in the posterior urethra. The somatic and visceral pudendal nerves (S2–S4) then stimulate rhythmic contraction of the ischiocavernosus and bulbocavernosus muscles, allowing ejaculation. Continued sympathetic stimulation ends the erection (**detumescence**) by inducing vasoconstriction of the arteries.

In women, orgasm involves "tenting" of the vagina (relaxation of the vaginal muscularis) and contractions of the pelvic diaphragm and uterus. Detumescence of the clitoral and vestibular erectile tissue is slower, which allows women to experience multiple orgasms.

FERTILIZATION

Successful fertilization depends on four sequential steps:

- Gamete delivery.
- Binding of the sperm.
- Activation of the egg.
- Fusion.

Ovulation occurs within 24–48 hours of the mid-cycle surge of LH. Usually, only one egg is released, entering the fallopian tube via ciliary action. The egg can survive only 24 hours in the female tract, so fertilization must occur around the time of ovulation.

By comparison, sperm can survive in the female tract for up to 5 days. In their journey to the fallopian tubes, they are aided by an estrogen-induced watery uterine mucus and peristaltic uterine contractions. Before being able to fertilize the egg, sperm must be **capacitated** in the female tract—a set of changes that alter membrane fluidity, membrane potential, and even movement of the tail.

Fertilization takes place in the fallopian tube. Capacitated sperm penetrate the corona radiata and bind to the zona pellucida. This species-specific interaction triggers the acrosome reaction and allows the entire sperm cell to burrow deeper into the egg.

CLINICAL CORRELATION

Fraternal (dizygotic) twins result when two eggs are released and fertilized. Identical (monozygotic) twins result when one fertilized egg divides and develops into two embryos.

The unfertilized egg is metabolically quiescent. After fusing with the sperm cell, the egg undergoes a signal transduction cascade that stimulates the egg to complete meiosis and releases cortical granules to prevent polyspermy (see Figure 9-40). Sperm already bound to the zona pellucida are removed, and new ones are prevented from binding. This is termed the "slow block" to polyspermy.

The egg's cytoplasm causes the sperm nucleus to decondense and form the male pronucleus. The mitochondria and tail disintegrate, but the sperm cell

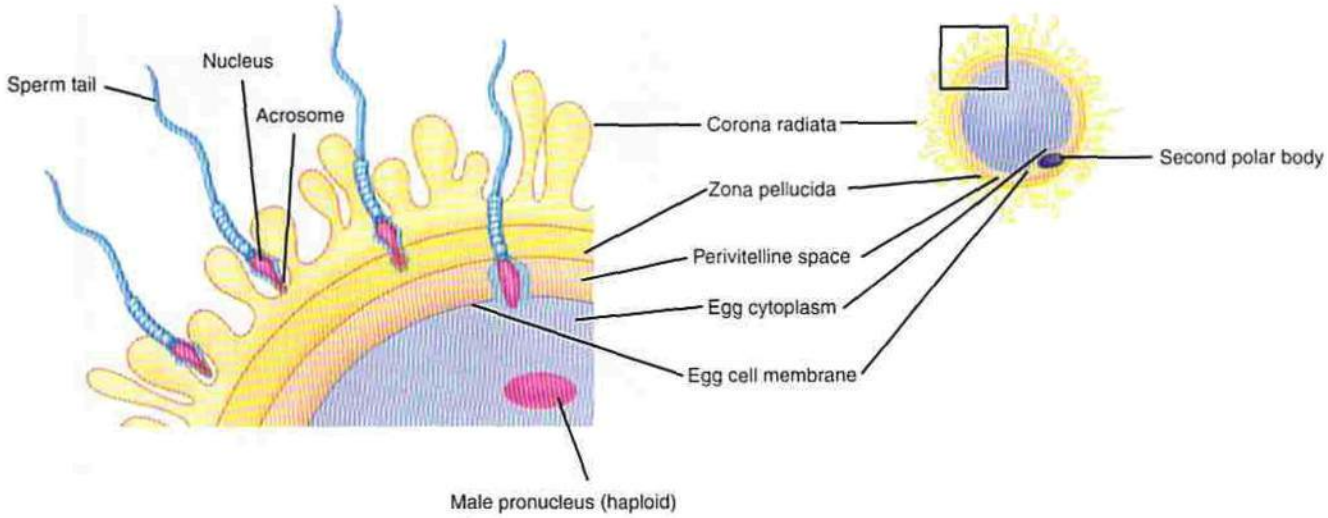


FIGURE 9-40. Penetration of a sperm cell into the ovum. The second polar body only appears after fertilization takes place.

contributes a centriole for cell division. The male and female centrioles organize an aster, allowing the two pronuclei to slowly come together over the course of 12 hours. During this time, DNA replication occurs. Thus, when the male and female pronuclei finally fuse, the zygote can undergo mitosis to form two diploid cells.

While undergoing cell division, the zygote travels down the oviduct to the uterus, where it implants 5 days after fertilization.

At best, the probability of fertilization is 35%, and only two-third of fertilized eggs develop successfully. Thus, the probability of a successful pregnancy is about 25%.

KEY FACT

Fertilization of a single egg with multiple sperm would result in aneuploidy, **not** multiple, viable zygotes.

CLINICAL CORRELATION

Ectopic pregnancies occur when the egg implants somewhere other than the uterus. Implantation in the fallopian tube can lead to tubal rupture.

PREGNANCY

Designed to optimize the welfare of the fetus, numerous metabolic and physical changes occur in the mother's body during pregnancy.

Osmoregulation

Pregnancy is a state of chronic volume overload and has many features similar to those of congestive heart failure, including edema and polyuria. The fetus, placenta, and amniotic fluid contribute about half of the 6- to 8-L increase in total body water. As Figure 9-41 illustrates, various factors favor Na^+ excretion or retention. Despite net Na^+ retention, serum levels (and plasma osmolality) actually decrease due to dilution. Similarly, hemodilution causes **physiologic anemia** and compensatory increased cardiac output.

Urinary System

Positioning of the fetus can lead to decreased bladder capacity and increased urinary frequency and incontinence. An additional effect of progesterone-mediated smooth muscle relaxation is dilation of the ureters. Secondary to fluid overload, the renal pelves/calyces also dilate, literally opening the kidneys up to infection. Volume overload dilutes the serum levels of blood urea nitrogen (BUN), creatinine, and uric acid, and increases the effective renal plasma flow and glomerular filtration rate (GFR). The renal tubular absorptive capac-

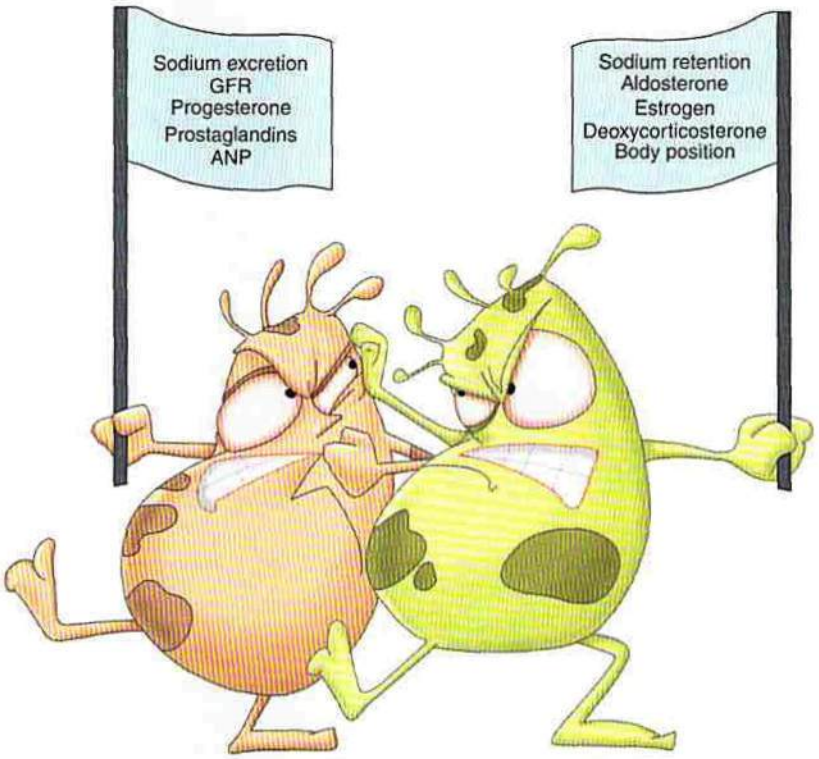


FIGURE 9-41. Factors for Na+ retention and excretion. ANP = atrial natriuretic peptide; GFR = glomerular filtration rate.

ity is surpassed, which may result in glucosuria (but not proteinuria). Similarly, small amounts of blood may also appear in the urine.

Cardiovascular System

Increased heart rate (HR) and stroke volume (SV) result in a 30%–50% increase in cardiac output (CO). Nonetheless, blood pressure (BP) actually decreases secondary to progesterone acting on smooth muscle to decrease systemic vascular resistance (SVR). By the third trimester, BP returns to baseline. A low-grade systolic flow murmur and mild left ventricular hypertrophy are other normal physiologic changes seen during pregnancy.

FLASH BACK

Remember:
CO = SV × HR
BP = CO × SVR

Though the mother's blood volume increases about 50%, plasma expands at a faster rate than RBC mass, hastening the development of physiologic anemia. Platelet count may also progressively decline (gestational thrombocytopenia). Nonetheless, due to increased fibrinogen, decreased protein S, and increased venous stasis in the legs, the mother is actually in a **hypercoagulable state**.

KEY FACT

The mother's respiratory rate (RR) generally remains unchanged; she hyperventilates without becoming tachypneic.

Respiratory System

Pregnancy results in elevation of the diaphragm, which decreases the residual volume. The total lung capacity (TLC) decreases only slightly, however. The net effect is decreased residual volume but increased inspiratory capacity. Notably, on spirometry testing, forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), are unchanged.

FLASH BACK

Remember: MV = TV × RR

These changes have no effect on respiratory muscle function itself. The tidal volume (TV) actually increases to allow for increased minute ventilation (MV) and chronic hyperventilation. Hyperventilation leads to decreased partial CO_2pressure, leading to chronic (mild) respiratory alkalosis and compen-

satory metabolic acidosis, which facilitate fetal off-loading of acidic wastes and CO_2.

On the negative side, estrogen can induce hyperemia and edema in the upper respiratory tract, which can lead to nasal stuffiness and epistaxis. Decreased pulmonary vascular resistance (PVR) and oncotic pressure can also lead to pulmonary edema.

Digestive System

Most changes to the digestive system are side effects of hemodilution and progesterone. Albumin and total protein levels appear decreased due to volume overload. Nonetheless, the body's new set-point favors Na^+ and water resorption in the large intestine. Progesterone reduces small bowel motility, further leading to constipation. Progesterone also delays gallbladder emptying, allowing for cholesterol saturation and the formation of gallstones. Smooth muscle relaxation of the lower esophageal sphincter leads to gastroesophageal reflux disease (GERD) and nausea. Lastly, portal hypertension, spider angiomas, and palmar erythema can mimic liver disease.

Endocrine System

Human placental lactogen (hPL) induces maternal insulin resistance to ensure continued transport of nutrients from mother to fetus. This leads to fasting hypoglycemia and postprandial hyperglycemia in the mother, in other words, glucose intolerance. With the body's response to insulin numbed, pancreatic β cell hypertrophy results in **hyperinsulinemia** and an increased risk of gestational diabetes.

Triglycerides (TGs), high- and low-density lipoprotein (HDLs and LDLs), and total cholesterol levels all increase during pregnancy, as they are necessary precursors for steroidogenesis in the maternal adrenal glands. Progesterone, a cortisol antagonist, prevents cushing-like effects that might otherwise be caused by increased adrenal function and delayed plasma clearance of cortisol.

Effects on the pituitary and thyroid are more subtle. Despite negative feedback by estradiol and progesterone (which decrease FSH and LH), the pituitary gland enlarges and increases its secretion of prolactin. Despite hCG mimicking the activity of thyroid stimulating hormone (TSH) in the first trimester and possible abnormal thyroid function tests, the mother remains euthyroid throughout the pregnancy. In other words, estrogen causes an increase in thyroglobulin (TGB) but free triiodothyronine (T_3) and thyroxine (T_4) levels remain relatively normal.

FLASH BACK

Do not confuse thyroglobulin (TGB) with thyroxine-binding globulin (TBG).

CLINICAL CORRELATION

Insufficient thyroid hormone levels during pregnancy, resulting from either a poorly functioning thyroid gland or low dietary iodine, can lead to severe neurologic and muscular problems in the fetus.

Estrogens

Mechanism

Suppresses ovulation, reduces LDL, raises HDL.

Types

- Natural: Premarin-conjugated estrogens.
- Steroidal: Ethinyl estradiol and mestranol.
- Nonsteroidal: Diethylstilbestrol (DES).

Uses

Hormone replacement therapy (HRT) in patients without breast cancer history; osteoporosis; birth control.

Side Effects

Nausea, weight gain, breast tenderness, thrombosis (predisposes to hypercoagulable state), endometrial hyperplasia, migraine, increased risk of endometrial cancer; DES increases risk of clear cell vaginal adenocarcinoma in offspring.

Other Estrogen-Related Drugs

Clomiphene

Mechanism

Estrogen receptor antagonist in hypothalamus → reduced negative feedback → increased ovulation.

Uses

Fertility.

Side Effects

Abdominal pain, breast tenderness, multiple births.

Tamoxifen

Mechanism

Partial agonist/antagonist (selective estrogen receptor modulator [SERM]) → agonist in endometrial tissue, but antagonist in breast tissue.

Uses

HRT in patients with family history of breast cancer.

Side Effects

Thrombosis, endometrial cancer, endometriosis, hair/nail thinning.

Raloxifene

Mechanism

Another SERM similar in action to tamoxifen, but also has antagonistic activity in endometrium.

Uses

Breast cancer; safe to use in patients with history of endometrial cancer.

Side Effects

Hot flashes, sudden sweating/warmth, increased vaginal discharge, joint/muscle pain, weight gain.

Progestins

Mechanism

Stimulates endometrial sloughing, suppresses ovulation.

Uses

Used with estrogens for birth control (see Table 9-10); stimulates appetite in cachectic patients.

Side Effects

Weight gain, hirsutism, acne, depression, decreased HDL, increased LDL.

TABLE 9-10. Progestin-Related Drugs

Drug	Mechanism of Action/Uses
Norplant	Time-release strip, implanted SC; slowly releases levonorgestrel into the body; provides contraception for up to 5 y.
RU-486	Progestin agonist/antagonist; used in emergency postcoital contraception.

Androgen Inhibitors

Cyproterone

Mechanism

Inhibits androgen activity in peripheral tissues.

Uses

Hirsutism.

Side Effects

Breast swelling, decreased libido; inability to have or keep an erection; excess milk flow from the breast.

Flutamide

Mechanism

Competitively antagonizes the testosterone receptor.

Uses

Prostate cancer.

Side Effects

Hot flashes, diarrhea, nausea, gynecomastia, impotence.

Finasteride

Mechanism

5 α-reductase inhibitor, decreases conversion of testosterone to DHT.

Uses

Benign prostatic hyperplasia; male pattern baldness.

Side Effects

Breast enlargement/tenderness, lip swelling, testicular pain, GI distress (diarrhea, abdominal pain).

Immune System

Changes to immune function during pregnancy are complex. Estrogen and cortisol cause a progressive rise in WBC count, mostly polymorphonuclear leukocytes. This preference for granulocytes over lymphocytes and monocytes favors humoral immunity over cell-mediated immunity. Progesterone, on the other hand, reduces the immune response, ostensibly to prevent rejection of the "foreign" fetus.

KEY FACT

Only IgG can cross the placenta.

CLINICAL CORRELATION

Whereas some autoimmune diseases may improve during pregnancy, others may worsen or cause fetal complications. For example, though lupus flares are uncommon in pregnancy, systemic lupus erythematosus (SLE) increases the risk of preeclampsia, preterm birth, and fetal death.

CLINICAL CORRELATION

If blood tests show an Rh-negative mother is carrying an Rh-positive fetus, she will be given anti–Rh factor (RHOgam) injections late in the pregnancy. Maternal anti–Rh factor antibodies do not affect the first Rh-positive fetus, but would put any future such pregnancies in jeopardy.

FLASH BACK

Remember: Screening tests (high sensitivity) are not designed to be diagnostic. However, a good screening test should lower the need for invasive diagnostic testing.

CLINICAL CORRELATION

hCG is also elevated in women with hydatidiform moles or choriocarcinoma.

CLINICAL CORRELATION

Failure of the placenta to properly implant in the uterine wall prevents dilation of the vessels, resulting in insufficient blood flow to the fetus and preeclampsia (hypertension, edema, and proteinuria) in the mother.

Skin and Bones

To maintain her center of gravity, a pregnant woman experiences increased spinal lordosis. In anticipation of the birthing process, the woman's pubic symphysis also widens. **Relaxin**, the peptide hormone responsible for this, causes relaxation of other ligaments as well.

Increased levels of active vitamin D [$1,25(OH)_2$] increase intestinal absorption of Ca^{2+} so it can be transported across the placenta. Calcitonin keeps Ca^{2+} resorption from becoming too overactive and attacking the maternal skeleton. Parathyroid hormone (PTH), on the other hand, is not particularly active because intestinal absorption keeps Ca^{2+} levels from falling too low. With all this, the maternal serum ionized Ca^{2+} and phosphate levels remain unchanged.

Some of the most obvious changes during pregnancy occur in the skin. Estrogen-induced angiogenesis accounts for facial flushing, and estrogen also plays a role in the tearing of collagen that leads to stretch marks. Separately, hyperinsulinemia may contribute to the **linea nigra** (a hyperpigmented band down the midline) and hirsutism.

Table 9-11 reviews the key physiologic changes during pregnancy in these organ systems.

Prenatal Testing

Standard prenatal screening tests include routine blood work, urinalysis, and ultrasound examinations. Other tests may be offered based on the mother's risk factors, such as age, race, and comorbidities.

Maternal serum **α-fetoprotein (AFP)** was one of the first screening tests developed. High levels suggest an open neural tube defect such as cephalocele or spina bifida, while low levels suggest Down's syndrome. The quad test, which makes use of multiple markers (AFP, estriol, hCG, and inhibin-A) is even more accurate (low false-positive rate).

Chorionic villus sampling (CVS) and amniocentesis are two common means of testing for chromosomal abnormalities. They are compared in Table 9-12.

The Placenta

Trophoblasts, cells forming the outer layer of the blastocyst, are the first cells to differentiate from the fertilized egg. They go on to develop into two layers: the inner cytotrophoblasts and outer syncytiotrophoblasts. The latter cells secrete hCG and attach to the uterine wall (endometrial stroma).

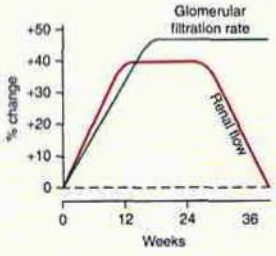
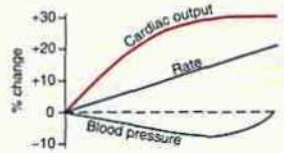
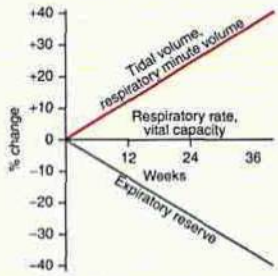
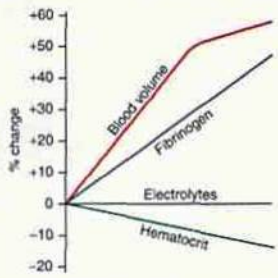
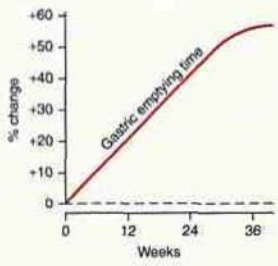
In the second trimester, the placenta takes over production of estrogen and progesterone, causing the corpus luteum to degrade into a corpus albicans. In the third trimester, the placental villi mature, promoting fetal/maternal exchange of nutrients.

The placenta is illustrated in Figure 9-42. Each gram of placenta can support 7 grams of fetal tissue.

Fetal Circulation

The fetal circulatory system is different from that of the adult. It must both make use of the maternal blood supply via the placenta and avoid overperfusing

TABLE 9-11. Maternal Adaptations to Pregnancy

System	Parameter	Pattern	
Renal	Renal flow	Increases 25–50%	
	Glomular filtration rate	Increases early, then plateaus	
Cardiovascular	Heart rate	Gradually increases 20%	
	Blood pressure	Gradually decreases 10% by 34 weeks, then increases to prepregnancy values	
	Stroke volume		
	Cardiac output	Increases to maximum at 19 weeks, then plateaus	
	Peripheral venous distention	Rises rapidly by 20%, then gradually increases an additional 10% by 28 weeks	
	Peripheral vascular resistance	Progressive increase to term	
		Progressive decrease to term	
Pulmonary	Respiratory rate	Unchanged	
	Tidal volume	Increases by 30–40%	
	Expiratory reserve	Gradual decrease	
	Vital capacity	Unchanged	
	Respiratory minute volume	Increases by 40%	
Blood	Volume	Increases by 50% in second trimester	
	Hematocrit	Decreases slightly	
	Fibrinogen	Increases	
	Electrolytes	Unchanged	
Gastrointestinal	Sphincter tone	Decreases	
	Gastric emptying time	Increases	
Weight	Uterine weight	Increases from about 60–70 g to about 900–1200 g	
	Body weight	Average 11-kg (25-lb) increase	

Modified, with permission, from Gardner DG, Shoback D, *Greenspan's Basic and Clinical Endocrinology*, 8th ed, New York: McGraw-Hill; 2007: 648.

TABLE 9-12. Diagnostic Testing for Chromosomal Abnormalities

	CVS	AMNIOCENTESIS
What is it?	Biopsy of rapidly dividing cells in the placenta.	Amniotic fluid retrieval of amniocytes.
When can it be done?	Early pregnancy (10–12 wks).	Mid-pregnancy (15–19 wks).
Risk of pregnancy loss?	1%	0.5%

CLINICAL CORRELATION

Though ABO blood type incompatibility occurs in approximately 20% of pregnancies, only a minority of these cases result in hemolytic anemia. Nonetheless, ABO blood type incompatibility is the most common cause of neonatal jaundice in the developed world.

the lungs while no gas exchange is occurring there. The three fetal shunts that allow this to occur are described in Table 9-13 and illustrated in Figure 9-43.

Furthermore, fetal hemoglobin (HbF) is more concentrated in fetal blood and has a greater affinity for O_2 than does maternal Hb. In other words, at any given partial oxygen pressure (P_{O_2}), HbF will have a greater O_2 saturation. This is possible because the γ subunit of HbF has a weaker positive charge than the adult β subunit, so 2,3-bisphosphoglycerate (2,3-BPG) has a weaker effect on lowering its O_2 affinity.

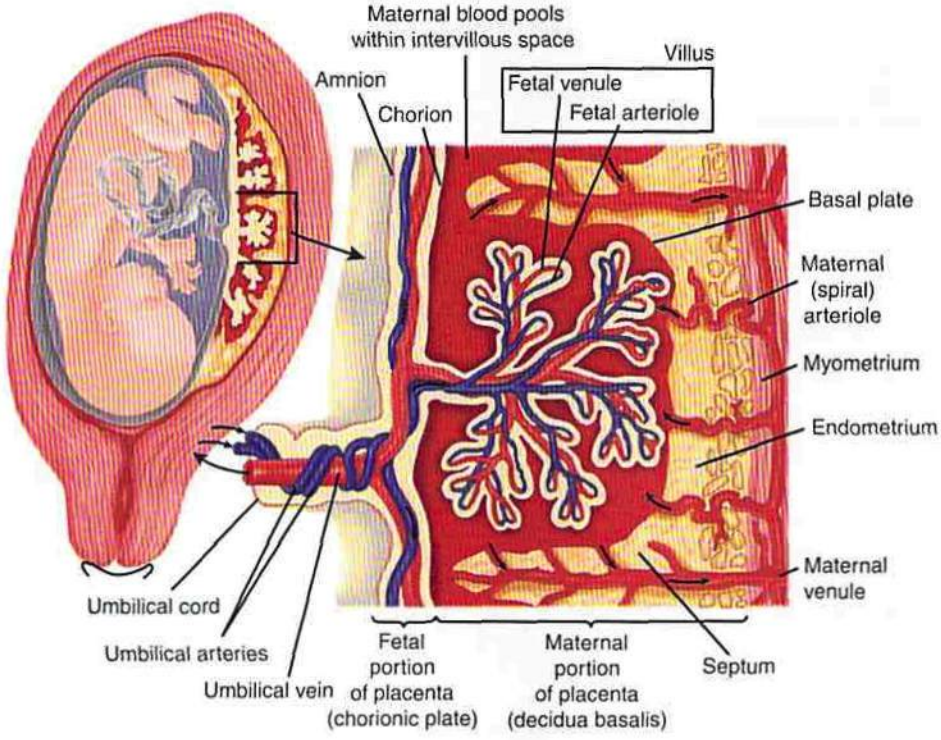


FIGURE 9-42. The mature placenta in cross-section. (Modified, with permission, from Morgan GE, Mikhail MS, Murry MJ, *Clinical Anesthesiology*, 4th ed, New York: McGraw-Hill; 2006: 880.)

TABLE 9-13. Shunts in the Fetal Circulation

Shunt	Ductus Arteriosus	Foramen Ovale	Ductus Venosus
Location	Between the aorta and pulmonary trunk (artery).	Between the RA and LA.	Connects umbilical vein to the IVC.
Function	Protects the lungs, allows the RV to strengthen.		Import maternal blood.
Flow	High PVR, low pulmonary blood flow.		Regulated by a sphincter.
Oxygenation	Mixed blood.		Oxygen-rich blood.

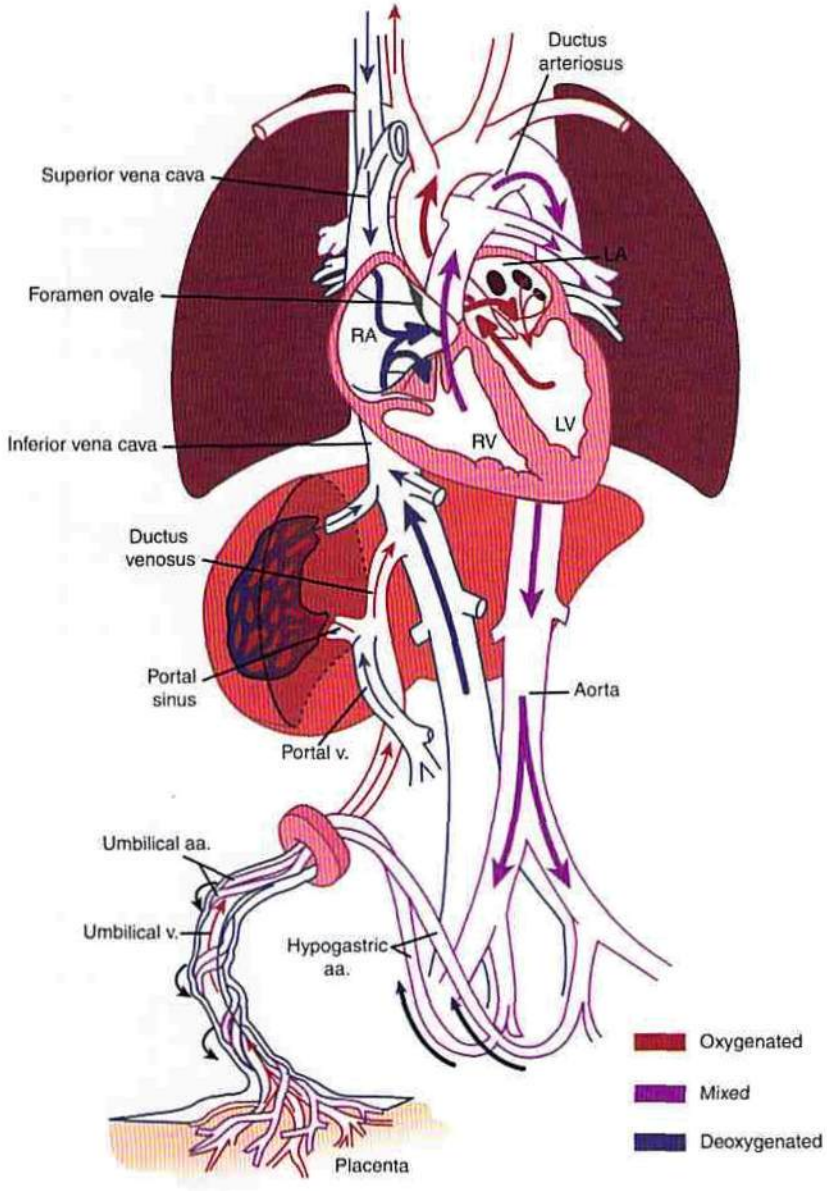


FIGURE 9-43. Fetal circulation. (Modified, with permission, from Cunningham FG, Leveno KL, Bloom SL, et al, *Williams Obstetrics*, 22nd ed, New York: McGraw-Hill; 2005: 103.)

KEY FACT

Ductus arteriosus: Most important in decreasing pulmonary blood flow.

Foramen ovale: Ensures that the developing brain gets oxygenated blood.

Ductus venosus: Bypasses the liver, preventing loss of nutrients.

FLASH BACK

Oxygenated blood flows into the IVC, then the foramen ovale, aorta, and head.
Deoxygenated blood flows into the superior vena cava (SVC).
Mixed blood flows into the pulmonary artery, then the ductus arteriosus and the lower body.

FLASH BACK

Increased O_2 affinity does not increase O_2 delivery. Instead, the RBC is less likely to give up the O_2. Acidic conditions and 2,3-BPG encourage O_2 release (right shift, or the Bohr effect).

KEY FACT

Inspiration increases Po_2 and causes release of bradykinin, two factors that close the ductus arteriosus. Indomethacin, a nonsteroidal anti-inflammatory drug, can also be used to close the shunt in hypoxic newborns.

KEY FACT

There is no direct contact between maternal and fetal blood.

CLINICAL CORRELATION

Maintaining a patent ductus arteriosus (PDA) with prostaglandins may actually be necessary in anatomic abnormalities such as coarctation of the aorta, transposition of the great arteries, and **tetralogy of Fallot**.

For an adult, these modifications are unnecessary. Thus, four key changes allow for the transition from fetal to normal adult circulation:

- PVR decreases.
- SVR increases.
- The fetal shunts close.
- Series circulation switches to parallel circulation.

Inspiration by the newborn causes vasoconstriction of the ductus venosus. Cutting off the placental blood supply causes portal blood to enter the hepatic sinusoids, resulting in a drop in BP in the IVC and right atrium (RA). Inspiration also causes the ductus arteriosus to close. Accompanied by reduced PVR from lung expansion, this results in increased pulmonary blood flow. The left atrial (LA) pressure rises and the RA pressure decreases, closing the foramen ovale, and thus functionally setting up the normal adult systemic circulation. Anatomic closure occurs with the formation of fibrous tissue.

KEY FACT

Monozygotic twins are always of the same gender.
Dizygotic twins can be the same or different genders.

Twinning

Multiple fetal gestation, though not a true pathologic state, is a natural cause of premature birth. The average gestational age for twins is 35 weeks, and for triplets it is 33 weeks.

CLINICAL CORRELATION

Having monozygotic twins is based on chance, whereas the likelihood of having dizygotic twins can be influenced by anything that increases fertility (eg, fertility drugs or increased FSH at either end of the reproductive lifetime). Thus, dizygotic twins may run in families, but monozygotic twins do not.

Fraternal (dizygotic) twins, which result from two fertilized ova, always have their own chorion and amniotic sac (see Figure 9-44). Identical (monozygotic) twins, born from a single ovum, usually share a chorion but have separate amniotic sacs. About one-third of monozygotic twins do have unique chorions and amniotic sacs, however, depending on when the ovum splits. Figure 9-45 illustrates this timeline.

Breast-Feeding

During pregnancy, estrogen and progesterone levels are high. These hormones ready the breasts for milk production. However, estrogen antagonizes prolactin, preventing lactation. After expulsion of the placenta, estrogen and progesterone levels drop, removing the blockade of prolactin. The suckling of an infant on the breast stimulates prolactin secretion from the anterior pitu-

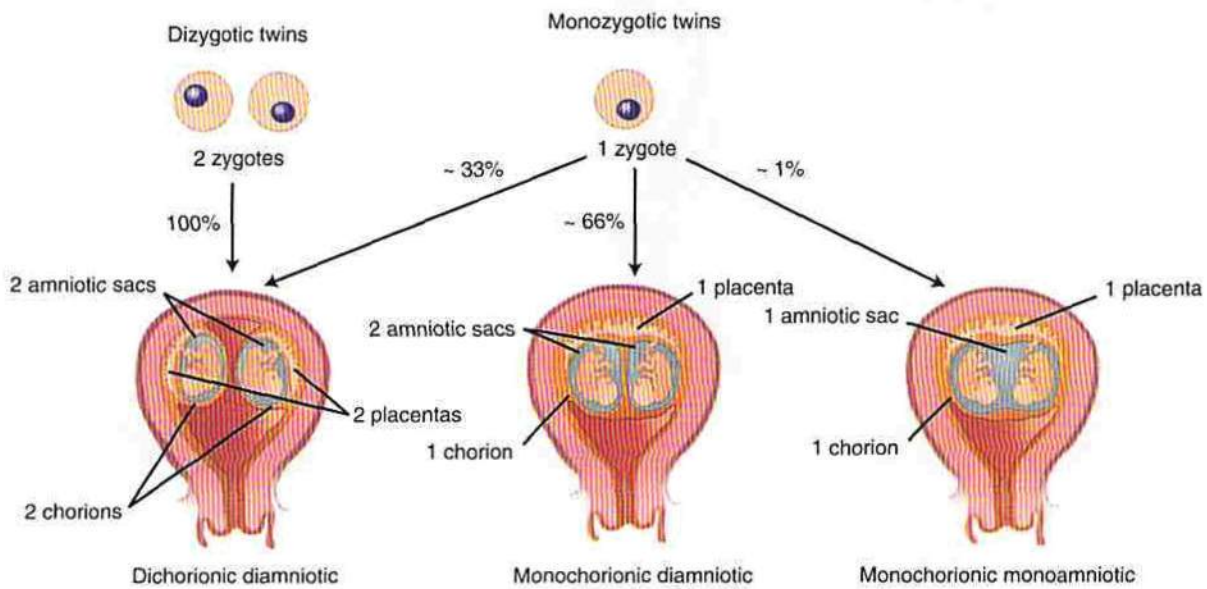


FIGURE 9-44. Development of dizygotic and monozygotic twins.

Incidence: 1:250 Pregnancies
Fetal sex: Same (except meiotic non-disjunction, e.g., xo, xy)
Fertilization: 1 sperm, 1 egg

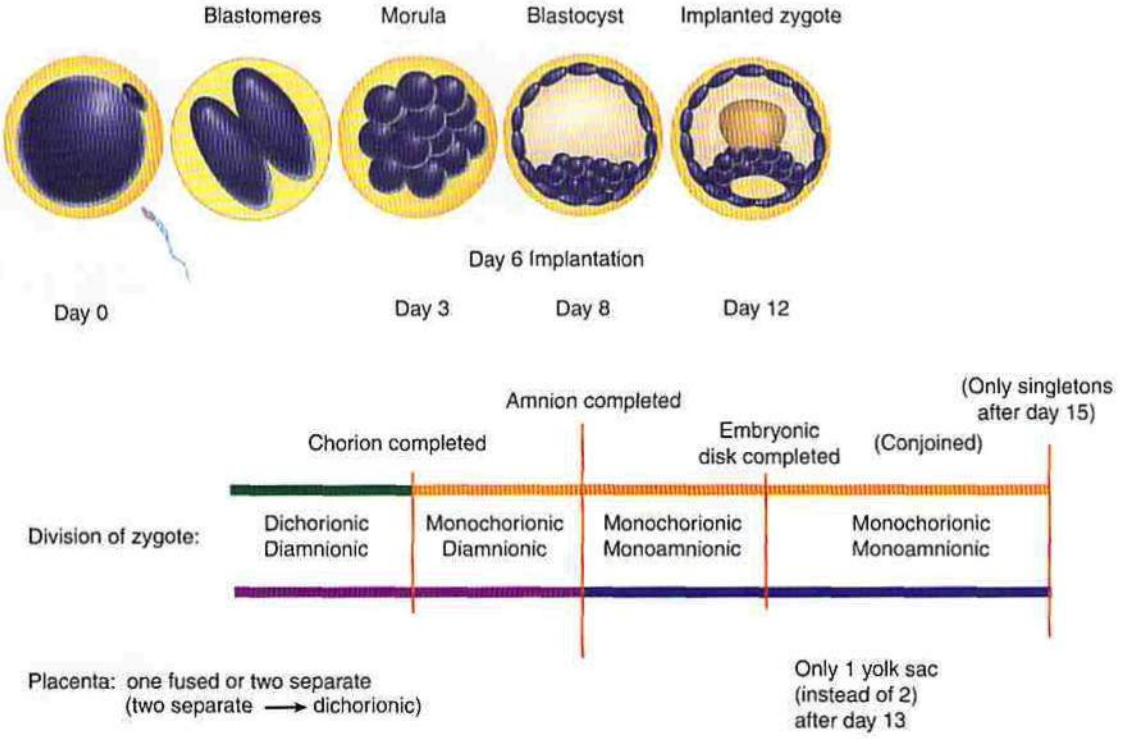


FIGURE 9-45. Chorionicity in monozygotic twins. Division of the zygote between days 12 and 15 results in conjoined twins.

itary and subsequent milk production. The posterior pituitary secretes **oxytocin**, which expels the milk into the lactiferous ducts (the milk "let-down" reflex).

Breast milk is a dynamic fluid that changes both throughout the day and over the course of lactation. For example, though the volume decreases over a single feeding, the fat content increases. Similarly, breast milk is particularly rich in immunoglobulins (IgA) within the first 5 days after delivery.

It is believed that breast-feeding reduces a child's chances of acquiring acute infections (eg, respiratory syncytial virus, GI infections, and otitis media), chronic illnesses (eg, leukemia, irritable bowel disease, and obesity), and allergies. Similarly, breast-feeding seems to reduce the mother's risk of ovarian and premenopausal breast cancer, as well as that of osteoporosis and anemia.

MENOPAUSE

The cessation of menstruation, menopause, occurs around age 52 and results from depletion of functional follicles in the ovaries. This leads to low serum levels of estradiol, elevated levels of FSH, and secondary amenorrhea. Some women experience other symptoms such as palpitations, joint pain, decreased libido, vaginal dryness, and poor sleep (leading to forgetfulness and irritability).

Estrogen hormone replacement therapy (HRT) counteracts many of these symptoms, positively affecting the CNS to improve cognition and reduce

KEY FACT

No twinning is possible 15 days after fertilization.

CLINICAL CORRELATION

Chorionicity in monozygotic twins can usually be determined by ultrasound. Some dichorionic, diamniotic gestations, however, feature a fused placenta, which falsely gives the appearance of a monochorionic, diamniotic pregnancy.

KEY FACT

Breast milk contains antimicrobial, immunomodulating, and anti-inflammatory agents not found in formula.

KEY FACT

Hormonal changes lead to reduced estrogen, higher FSH, higher LH (no surges), and higher GnRH.

MNEMONIC

Menopause creates ***HAVOC.***

Hot flashes
Atrophy of the
Vagina
Osteoporosis
Coronary artery disease

KEY FACT

Each additional X chromosome correlates with an increasingly abnormal phenotype and with more severe mental retardation.

FLASH BACK

Maternal meiotic nondisjunction may result in an egg containing two X chromosomes.

depression. Estrogen therapy also preserves bone mass and inhibits hot flashes. However, unbalanced oral estrogen therapy increases a woman's risk of thromboembolic phenomena, stroke, and endometrial cancer. Similarly, estrogen-progesterone therapy (EPT), which reduces the risk of colorectal cancer, increases the risk of breast cancer and coronary heart disease. Development of these negative effects, of course, depends on the length of HRT and the age at which it is given.

Pathology—Male

GENETIC DISEASES

Klinefelter's Syndrome

Seen in males with an extra X chromosome (47,XXY), Klinefelter's syndrome affects 1 in 500–1000 male births. It is most commonly due to maternal meiotic nondisjunction and correlates positively with increasing maternal age. It is associated with autoimmune disorders like SLE, RA, and Sjögren's syndrome.

Presentation

- Hypogonadism (i.e., small, firm testes due to fibrosis and hyalinization) and infertility due to azoospermia.
- Gynecomastia at puberty due to an abnormal testosterone:estradiol ratio.
- Elevated urinary gonadotropins result from lack of feedback inhibition by the pituitary gland.

Diagnosis

- Klinefelter's syndrome is suggested by classic phenotypic findings including gynecomastia, tall stature, and small and firm testes.
- Hormonal findings include decreased testosterone and elevated estrogen and gonadotropin levels (FSH and LH).
- Confirmed by demonstrating (classically) a 47,XXY karyotype.

Treatment

- Testosterone therapy is initiated in individuals in whom puberty is delayed, fails to progress, or when there is a low testosterone level.
- Most individuals receive life-long testosterone therapy.
- While previously believed to be infertile, many Klinefelter's patients can now be rendered fertile by advanced fertility techniques, such as testicular biopsy to retrieve sperm from the testes, and intracytoplasmic sperm injection (ICSI), whereby one sperm is directly injected into each egg that has been retrieved from a woman's ovaries during an in vitro fertilization (IVF) cycle.

XYY Chromosomes

- Phenotypically normal male.
- Results from paternal nondisjunction at meiosis I, resulting in a sperm with an extra Y chromosome.
- XYY occurs 1 in 1000 male births.

- Increased risk of learning disabilities (speech and language skills) and behavioral problems.
- Reports of increased proportion of XYY males in prisons and mental hospitals is now known to be incorrect.
- Often are several centimeters taller than parents and siblings and have severe acne.

Male Pseudohermaphrodite

Genetic male (46,XY) with female external genitalia. Testes are present. However, there is effective testosterone deficiency, possibly due to any of the following:

- Defective testicular differentiation.
- Impaired secretion/production of testosterone.
- Failure of conversion of testosterone to dihydrotestosterone.
- Defect of androgen receptors.

5α-Reductase Deficiency

- An enzyme, α-reductase converts testosterone to dihydrotestosterone, a potent androgen required for the development of male external genitalia.
- Males born with this enzyme deficiency have testes with female or ambiguous **external genitalia**.
- Since functioning testes produce testosterone and MIS, **internal genitalia** develop in a male pattern.

Androgen Insensitivity

- Mutations occur at the level of androgen receptors, rendering them inactive. Testes are normal and produce testosterone, MIS, and other substances.
- Males with androgen insensitivity present with failure of development of male internal and external genitalia.
- Presence of MIS prevents development of uterus and fallopian tubes.
- **Complete** androgen insensitivity results in normal female external genitalia, while **incomplete** androgen insensitivity results in ambiguous external genitalia.

True Hermaphrodite

- Presence of both ovaries and testes in the same individual, which may be due to XX/XY mosaicism or abnormal crossover of a portion of a Y chromosome with the *SRY* region to the X chromosome.
- The external genitalia may range from normal male, to ambiguous, to normal female.
- The most common type of external genitalia is ambiguous genitalia.
- Cryptorchidism and hypospadias are common.
- The gonads may be ovotestes (**most common**), followed by ovaries and, least commonly, testes.
- The development of the genital ducts follows that of the ipsilateral gonad.
- Germ cell tumors, inguinal hernias, and obstructed genital tracts frequently occur in true hermaphrodites.

MNEMONIC

Nomenclature for **PSEUDO**hermaphrodite is named after the **GONAD** present (i.e., if testes are present, the subject is a **MALE** pseudohermaphrodite).

FLASH BACK

Formation of gonads (testes or ovaries) is genetically determined, while formation of male external genitalia is determined by the presence of functional testes; in the absence of functioning testes, development is female.

KEY FACT

Dihydrotestosterone is responsible for virilization of male external genitalia and secondary sexual characteristics.

KEY FACT

Testosterone is required for ipsilateral wolffian duct development.

KEY FACT

Mosaicism is the presence of two different populations of cells with different genotype in one individual.

FLASH BACK

Syphilis is caused by the spirochete ***Treponema pallidum***. It can be identified by dark-field microscopy.

FLASH BACK

Gonorrhea is caused by an intracellular gram-negative diplococcus, ***Neisseria gonorrhoeae***. It must be cultured on Thayer-Martin (VCN) media to be identified.

FLASH BACK

Chlamydia infection is caused by the obligate intracellular parasite ***Chlamydia trachomatis***. A lab diagnosis can be made by observing cytoplasmic inclusions on a Giemsa or fluorescent-antibody stained smear.

KEY FACT

Phimosis is prone to infection, commonly due to ***Candida***.

PENILE DISEASES

Congenital Abnormalities

Congenital Inguinal Hernia

- Outpouching or protrusion of abdominal cavity contents into the inguinal canal through a persistent processus vaginalis.
- The processus is derived from posterior parietal peritoneum, which invaginates and migrates toward the scrotum through the inguinal canal.
- Failure of such obliteration results in the formation of a sac through which abdominal cavity contents herniate.
- Also known as an indirect inguinal hernia.
- Anatomically, congenital inguinal hernia lies **lateral to the inferior epigastric vessels** (see Figure 9-46).
- Associated with hypospadias, epispadias, cryptorchidism, and ambiguous genitalia.
- This condition affects males more than females with a ratio of 48:1.
- Surgery is recommended to prevent incarceration.

Infectious Diseases

Table 9-14 shows etiology, transmission, symptoms, and complications of common infectious diseases of the penis.

Other Abnormalities

Phimosis

Extremely tight foreskin that is too small to be retracted over the glans penis. While a physiologic state until 3 years of age, after that it is considered pathologic. Often occurs in uncircumcised males that experience chronic infections and inflammation of the glans penis (**balanitis**), sometimes due to poor hygiene of the area. Circumcision can be used as a treatment after the initial infection is treated with broad-spectrum antibiotics.

Peyronie's Disease

A dense, subcutaneous fibrous plaque forms on the tunica albuginea on the dorsal side of the penis, which causes the penis to curve laterally when erect. The etiology of the plaque formation is unknown, but it most often affects

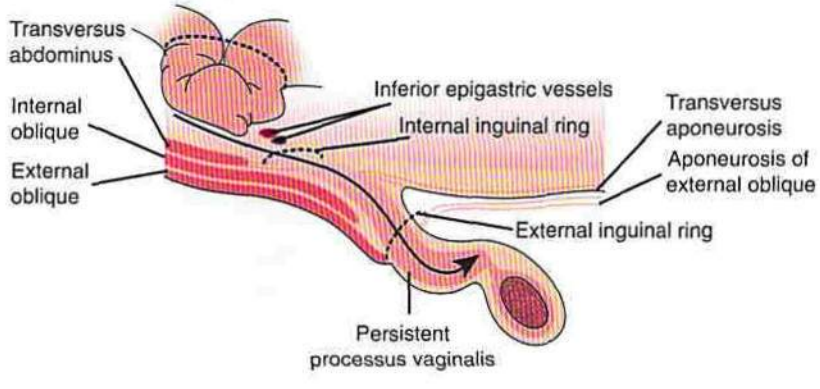


FIGURE 9-46. Indirect inguinal hernia. Note that the hernia lies lateral to the inferior epigastric vessels. (Modified, with permission, from Tintinalli JE, Kelen GD, Stapczynski JS, et al, *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 6th ed, New York: McGraw-Hill; 2004.)

TABLE 9-14. Infectious Diseases of the Penis

Disease (Organism)	Transmission	Symptoms	Complications
Syphilis (*Treponema pallidum*).	Sexually transmitted	Primary syphilis: Painless chancre on penis (if painful, chancroid).	Secondary syphilis : Systemic disease ▪ Maculopapular rash. ▪ Condylomata lata. ▪ Constitutional symptoms. Tertiary syphilis: ▪ Skin/bone gummas. ▪ Aortitis. ▪ Tabes dorsalis. ▪ Argyll Robertson pupil.
Gonorrhea (*Neisseria gonorrhoeae*).	Sexually transmitted	▪ Urethritis. ▪ Prostatitis. ▪ Creamy purulent penile discharge. ▪ Arthritis.	▪ Epididymitis. ▪ Can very rarely cause infection of the testes.
Chlamydia (*Chlamydia trachomatis* [D–K] [serotypes L1, 2, and 3 cause lymphogranuloma venereum, and serotypes A, B, and C cause trachoma]).	Sexually transmitted	▪ Urethritis. ▪ Conjunctivitis. ▪ Reiter's syndrome.	▪ Epididymitis.

older men. If the curvature of the penis interferes with normal sexual intercourse, surgical correction is recommended. If erectile dysfunction or infertility occurs, then a penile implant should be considered.

Priapism

An erection that is persistent and often very painful. Can be a result of sickle cell disease, spinal cord injury, antidepressants, antipsychotics (especially chlorpromazine and trazodone), and penile trauma.

KEY FACT

Trazodone can cause a painful erection.

Balanitis

Inflammation of the glans penis. When the foreskin and prepuce are also inflamed it is called **balanoposthitis**. Balanitis is commonly seen in unhygienic uncircumcised men. The collection of smegma, which is carcinogenic, and the lack of aeration causes irritation and inflammation, accounting for the increased rates of penile cancer seen in uncircumcised males. Balanitis can be complicated by phimosis and meatal stenosis leading to urinary retention. Treatment includes cleaning of the area and antibiotics.

Bowen's Disease

Intraepithelial neoplasia on the shaft of penis/scrotum. It is also known as **erythroplasia of Queyrat** or **in situ carcinoma** of the penis. It is a precancerous lesion and has a **10% chance of progression to carcinoma**.

Bowenoid Papulosis

Small, multiple, red-, brown-, or flesh-colored patches on the skin of the penis. It is a **premalignant** condition with a 2%–3% chance of progression to

cancer. Bowenoid papulosis has a close link to HPV and is described as being between genital warts and Bowen's disease of the penis in severity. Many cases of Bowenoid papulosis spontaneously regress, but close follow-up is required, as it has malignant potential.

Cancer

Squamous cell carcinoma of the penis. Penile cancer is rare in the United States, representing < 1% of cancers in males. Penile cancer is frequently seen in an uncircumcised, unhygienic individual and is closely linked with genital warts and HPV.

DISEASES OF THE TESTES

Congenital Abnormalities

Cryptorchidism

- A failure of one or both testes to descend into the scrotal sac.
- Most often unilateral, though commonly occurring bilaterally, the undescended testis can frequently be palpated as a mass in the inguinal canal.
- A **greatly increased risk of germ cell tumors**, usually seminomas and embryonal carcinomas, are associated with cryptorchidism, even after surgical intervention, and in both the normal testis and cryptorchid testis.
- **Complications:** Ipsilateral inguinal hernia, testicular torsion, trauma, and infertility.
- **Treatment:** Orchiopexy decreases the risk of cancer if done prior to 10 years of age. It helps to fix the testes, prevent torsion, and increase fertility, and aids in detection of cancer because the external testis facilitates examination and diagnostics.

Infectious Diseases

Orchitis

An inflammation of the testes usually caused by the mumps virus and usually affecting only one testis.

- If the condition is **bilateral (uncommon)**, it **may lead to sterility** resulting from the atrophy of the seminiferous tubules. In the case of sterility, levels of testosterone will be decreased, but levels of FSH and LH will be increased.

Epididymitis

An infection of the epididymis that can be caused by a variety of bacteria.

- < 35 years old: *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.
- > 35 years old: *Escherichia coli* and *Pseudomonas aeruginosa*.
- A tuberculous infection can start in the epididymis and travel to the seminal vesicles, prostate, and testicles.
- Patients often suffer from pain and swelling in the scrotum, tenderness, and a positive **Prehn's sign** (a marked decrease in pain in association with elevation of the scrotum).

KEY FACT

Epididymitis is more common in men 19–40 years of age and orchitis is more common in a younger person (< 10 years).

Other Abnormalities

Torsion

A twisting of the spermatic cord that compromises blood supply to the testes, potentially resulting in testicular infarction and gangrene (see Figure 9-47).

- Most often caused by violent trauma to the testes or cryptorchidism.
- **Surgical correction** within 6 hours of occurrence usually results in full recovery of the testis.

Varicocele

Dilated and tortuous veins located in the pampiniform plexus of the spermatic cord that most often appears as a **"bag of worms"** on examination.

- The left testis is more likely to have a varicocele because its pampiniform plexus drains into the left renal vein before the IVC, causing increased pressure in the venous plexus. Normally, the left testis is slightly lower than the right testis.
- Any type of **obstruction of the left renal vein**, such as in renal cell carcinoma, can cause a varicocele.
- Varicocele is the most common cause of treatable male **subfertility**.

FLASH BACK

Unlike the right, the left testicular vein drains into the left renal vein instead of the IVC at a right angle.

Hydrocele

A collection of serous fluid that distends the tunica vaginalis. Most commonly caused by a **persistent tunica vaginalis** that communicates with the peritoneal cavity, but can also be due to infection or lymphatic blockage as a result of a tumor.

- Is the most frequent cause of **enlargement of the scrotum** in young boys.
- Can be distinguished from tumors by transillumination (see Figure 9-48). Hydroceles transilluminate; tumors do not.

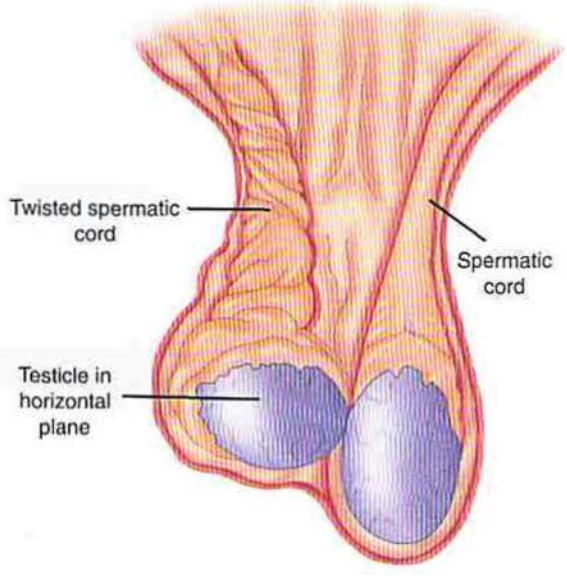


FIGURE 9-47. Testicular torsion. Note the unilateral pulling of the testis into the horizontal plane due to the twisting of the spermatic cord.

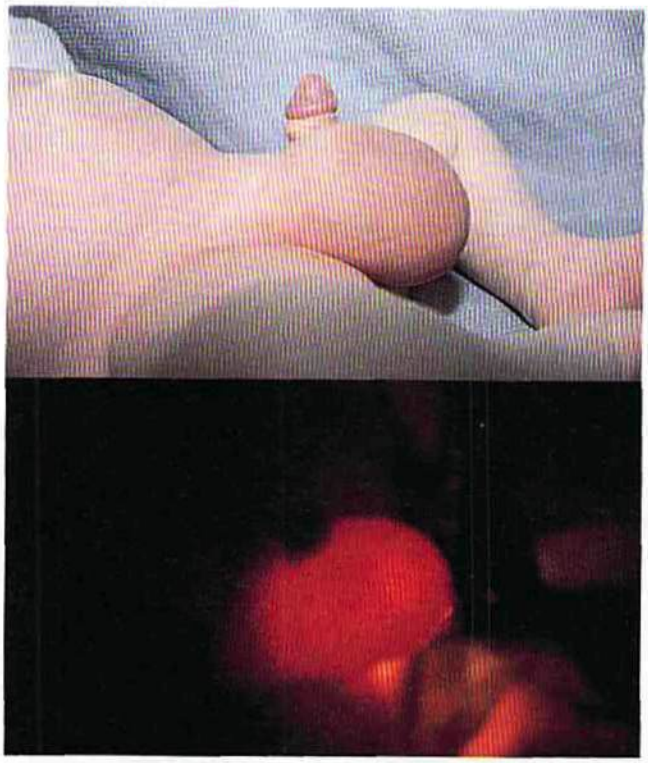


FIGURE 9-48. Hydrocele and transillumination. Note the translucent appearance when a light is shone through the testis filled with serous fluid. (Courtesy of Michael J. Nowicki, MD.)

HEMATOCELE

A collection of blood in the tunica vaginalis. Hematocele often results from testicular trauma and presents with pain, tenderness, and absent transillumination. They sometimes result from tapping a hydrocele during examination. If a hematocele is not drained, a clotted hematocele is formed which requires orchidectomy.

SPERMATOCELE

A collection of spermatozoa in the epididymis. Spermatocele is often present in the head of the epididymis and behind the upper pole of the testis. Small ones can be ignored while larger ones should be aspirated or excised through a scrotal incision.

NEOPLASMS

Germ Cell Tumors

KEY FACT

Cryptorchidism results in an increased risk of seminomas.

SEMINOMA (50%)

Large, soft, well-demarcated, gray-white tumor that bulges from the cut surface of the affected testis. A seminoma is confined beneath an intact tunica albuginea. Microscopically, large cells with distinct cell borders, pale nuclei, prominent nucleoli, and a sparse lymphocytic infiltrate are seen. Seminoma is **associated with an increase in hCG**. Seminoma uniquely metastasizes via the lymphatics, and is radiosensitive with an excellent prognosis (see Table 9-15).

TABLE 9-15. Characteristics and Prognosis of Seminoma, Yolk Sac Tumor, and Embryonal Carcinoma

MALIGNANCY	CHARACTERISTICS	PROGNOSIS
Seminoma	Increased hCG and a large, well-demarcated mass.	Excellent
Yolk sac tumor	Increased AFP and Schiller-Duval bodies.	Good
Embryonal carcinoma	Increased hCG and ill-defined masses with foci of necrosis and hemorrhage.	Poor

YOLK SAC TUMOR

Large, may be well demarcated. Microscopically, cells appear as low cuboidal to columnar epithelium forming sheets, glands, papillae, and microcysts, and are often associated with **hyaline globules**. This is the most common primary testicular neoplasm in children < 3 years. **α-Fetoprotein (AFP)** can be demonstrated within the cytoplasm of these neoplastic cells.

KEY FACT

Schiller-Duval bodies: Structures resembling primitive glomeruli, a distinctive feature of yolk sac tumors.

EMBRYONAL CARCINOMA

Ill-defined invasive mass containing foci of hemorrhage and necrosis. Metastases are common. Histologically, the cells are large and primitive looking, with basophilic cytoplasm, indistinct cell borders, and large nuclei with prominent nucleoli. The cells may be arranged in undifferentiated, solid sheets or glandular structures. **Embryonal carcinoma is associated with an increase in hCG.**

CHORIOCARCINOMA

Grossly, primary tumor is small and nonpalpable. Microscopically, choriocarcinoma is composed of sheets of small cuboidal cells irregularly intermingled with or capped by large, eosinophilic syncytial cells containing multiple dark, pleomorphic nuclei; **these represent cytotrophoblastic and syncytiotrophoblastic differentiation, respectively. hCG is elevated.**

TERATOMAS

Differentiated neoplastic germ cells along somatic cell lines. Teratomas are firm masses that on cut surface often contain cysts and recognizable areas of cartilage. Histologically, there are three major variants: mature, immature, and with malignant transformation, plus a mixed type.

- **Mature:** Fully differentiated tissues from one or more germ cell layers (neural tissue, cartilage, adipose, bone, and epithelium) in a haphazard array.
- **Immature:** Immature somatic elements reminiscent of those in developing fetal tissue.
- **With malignant transformation:** Characterized by the development of frank malignancy in pre-existing teratomatous elements, usually in the form of a squamous cell or adenocarcinoma. Usually occurs in adults.
- **Mixed:** Combinations of any of the described patterns may occur in mixed tumors, the most common of which is a combination of teratoma, embryonal carcinoma, and yolk sac tumors. **hCG and AFP are elevated.**

Interstitial (Non-Germ) Cell Tumors

Leydig's Cell Tumor

Arises from Leydig's cells, **contains Reinke's crystals**, and is benign in nature. It produces androgen, leading to gynecomastia in men and precocious puberty in boys. Treatment is orchidectomy.

Sertoli's Cell Tumor

Arises from Sertoli's cells. It produces feminization, leading to gynecomastia, loss of libido, and aspermia. It is a benign condition and orchidectomy cures.

PROSTATE DISEASES

Prostatitis

Inflammation of the prostate gland.

Presentation

- Dysuria, urinary frequency, lower back pain.
- Poorly localized pelvic pain.
- May be acute or chronic.
  - **Acute:** Caused by *E. coli* and other gram-negative rods. Neutrophilic infiltrate, congestion, and edema. Microabscesses may form. The prostate is often **tender and boggy**. Leukocytosis and fever are also seen.
  - **Chronic:** Tissue destruction, **increased fibroblasts**, and inflammatory cells. Can be caused by recurrent UTIs or STDs. There are two types of chronic prostatitis:
    - **Bacterial:** Same organisms responsible for acute prostatitis.
    - **Abacterial:** The most common form of chronic prostatitis. Leukocytes are found in prostatic secretions but there are no bacteriologic findings. There is no history of recurrent UTI. However, *Chlamydia trachomatis* and *Ureaplasma urealyticum* have also been implicated.

KEY FACT

More than 10 leukocytes/high power field without bacteria or positive cultures equals abacterial prostatitis.

Treatment

Trimethoprim-sulfamethoxazole or ciprofloxacin.

Benign Prostatic Hyperplasia

Benign enlargement of the prostate gland due to cellular proliferation, usually at the central zone (see Figure 9-49).

- It is commonly seen in males > 50 years of age.
- Family history (first-degree relatives) is a risk factor.
- With age, estrogen levels tend to increase, in turn inducing surface expression of androgen receptors in the central zone of the prostate. Therefore, despite the generally lower androgen levels in older men, their prostate hypertrophies because of increased **sensitivity** to dihydrotestosterone (DHT).

Presentation

Patient presents with urgency, frequency, nocturia, dribbling of urine, poor stream, sensation of incomplete voiding, incontinence, and urinary retention and often UTI.

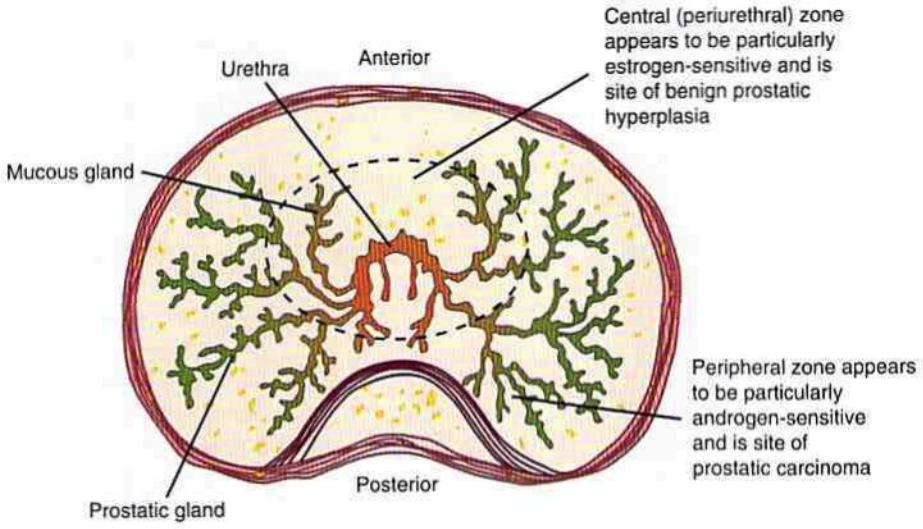


FIGURE 9-49. Transverse section of prostate showing location of BPH and prostatic carcinoma. The central portion of the prostate is sensitive to estrogen and is the site for BPH, while the peripheral zone is sensitive to androgen and is the site for prostatic carcinoma.

Diagnosis

- Firm, smooth, and uniform enlargement of the prostate on digital rectal examination.
- Sonogram shows a diffusely enlarged prostate.
- Prostate-specific antigen (PSA) level is checked to rule out prostate cancer.

Treatment

Medical treatment includes nonselective α-blockers (doxazosin, prazosin, and terazosin), selective α-blockers (tamsulosin), and 5α-reductase inhibitors (finasteride). Surgical management involves transurethral resection of the prostate (TURP) or prostatectomy.

Adenocarcinoma of the Prostate

- Arises mostly from the peripheral zone (70%) of the prostate.
- It occurs in 20%–30% of men > 50 years of age and in 90% of men > 70 years of age.
- Most are very slow growing and never present in the man's lifetime.
- With advancing age, the androgen level declines and the peripheral zone is the one that is most sensitive to the changes in the androgen level. **When the androgen level declines, regressive changes occur, mostly in the peripheral zone, and prostatic carcinoma arises in these settings.**

Presentation

- Appears as a hard, irregular mass during rectal examination.
- PSA is also elevated.

Spread

- Spreads via hematogenous or lymphatic channels and by direct invasion.
- Spreads to the lungs hematogenously and via the vertebral venous plexus to pelvic bones and lumbosacral spine.

FLASH FORWARD

Prazosin, doxazosin, and terazosin relax the bladder neck and prostate by blocking α-adrenergic receptors located in smooth muscle.

FLASH FORWARD

The 5α-reductase inhibitor finasteride inhibits conversion of testosterone to dihydrotestosterone. Dihydrotestosterone causes increased proliferation of smooth muscle in the central zone of the prostate.

FLASH BACK

PSA is a glycoprotein produced by both the normal and abnormal prostatic ductal epithelium and concentrated in the seminal vesicles. It liquefies the seminal coagulum formed during ejaculation.

FLASH BACK

The prostatic venous plexus and vertebral venous plexus have direct communication. Therefore, lumbosacral vertebrae and pelvic bones are common and early sites for metastasis.

KEY FACT

PSA is often used to monitor tumor burden and recurrences.

KEY FACT

Rectal exams do NOT increase the false-positive rate of PSA.

FLASH FORWARD

Flutamide is an androgen antagonist that blocks the androgen receptors.

FLASH BACK

Indifferent gonads will develop into ovaries without the genetic signal (aka "genetic switch") to turn into testes. This "genetic switch" is ***SRY***. If no germ cells are present in the indifferent gonad, it will fail to develop and will become a streak gonad.

KEY FACT

Turner's syndrome is the most common cause of primary amenorrhea.

- Lymphatic spread occurs to presacral, internal iliac, para-aortic, and supraclavicular nodes, while direct spread may invade the bladder, ureter, seminal vesicles, and other pelvic structures.
- The rectum is rarely involved due to the presence of the rectovesical fascia.

Diagnosis

- On digital rectal examination, the prostate appears to be **stony hard with obliteration of the median sulcus.**
- **PSA** > 10 ng/mL is suggestive and > 35 ng/mL is diagnostic of advanced cancer.
- **Alkaline phosphatase** is elevated either due to hepatic or bone metastasis.
- Radiologic findings in case of metastasis include characteristic sclerotic metastases in lumbar vertebrae and pelvic bones. However, osteolytic metastases are also common. Transrectal prostatic biopsy always confirms the diagnosis when in doubt.

Treatment

Radical prostatectomy can be done as a curative treatment for early disease, while palliative treatment is the only option for advanced disease. The palliative treatment involves deprivation of androgens via bilateral orchidectomy or by giving antiandrogens like flutamide. Other treatment options include radiation and GnRH agonists.

Pathology—Female

GENETIC DISEASES

Turner's Syndrome

Primary hypogonadism in phenotypic females resulting from partial (missing only the short arm of one X chromosome) or complete monosomy (XO). There is either primary amenorrhea/primary ovarian failure or premature ovarian failure (premature menopause before age 40), often at a very young age, with streak gonads. If there is any Y chromosome mosaicism, there is increased risk for gonadoblastoma (germ cell tumor) and gonadal extirpation is required.

Presentation

Newborns may have webbed neck, edema of the hands and feet, coarctation of the aorta, and characteristic triangular facies.

- Affected girls often fail to develop secondary sex characteristics.
- The genitalia may remain infantile with little pubic hair.
- Generally a short stature with a "shield chest" with widely spaced nipples streak ovaries, and amenorrhea.
- Short stature and primary amenorrhea in adult patients should prompt strong suspicion of Turner's syndrome.

Diagnosis

Karyotyping, high FSH:LH ratio.

Treatment

Teenage patients need counseling regarding stigmata of their condition and for hormone therapy. Estrogen is given for development of secondary sexual characteristics, normal menstruation, and osteoporosis prevention. Growth hormone may be given to increase the height of affected patients.

Prognosis

Patients with 45,X or 45,X mosaicism have a low fertility rate. Those who become pregnant have increased rates of spontaneous abortion (30%) and stillbirths (6%–10%).

Female Pseudohermaphrodite

- Genetic females with virilized or ambiguous external genitalia due to exposure to androgens during the eighth to 13th weeks of gestation.
- Commonly seen in congenital adrenal hyperplasia.

FLASH BACK

Fused lower ends of the müllerian duct forms the uterus, cervix, and upper two-thirds of the vagina.

Müllerian Agenesis

Characterized by a shortened vagina with absence of a uterus; however, a small rudimentary uterus may be noted. It is the second most common cause of primary amenorrhea.

The incidence rate is 1 in 4000–5000 live female births. Affected individuals have normal ovaries, and normal secondary sexual characteristics. The exact etiology is not known.

KEY FACT

The stratified squamous epithelium of the anus and vagina are derived from the cloaca. These have somatic innervation from the pudendal nerve. The structures superior have **columnar epithelium and visceral innervation.**

Presentation

- Primary amenorrhea in the presence of normal secondary sexual characteristics.
- The vagina may be absent or shortened.
- The labia majora, labia minora, and clitoris are normal.
- Ectopic kidneys are common. Others may present with voiding difficulties, recurrent UTIs, and urinary incontinence.

Diagnosis

- Ultrasound or MRI can often make the diagnosis.
- Laparoscopy is performed if there is an unclear diagnosis or pain from functioning obstructed müllerian remnants, possibly with a higher rate of endometriosis.
- A pyelogram is performed to assess frequently associated urinary tract abnormalities.

Treatment

- Progressive dilation or reconstructive surgery on the foreshortened vagina can be done to make the vagina more functional, and this may establish sexual functioning. Sometimes intercourse itself can serve this same purpose.
- Rudimentary uterine horns may need to be excised to prevent pain if they have functioning endometrium.

KEY FACT

Renal abnormalities are found in 20%–30% of women with müllerian duct abnormalities.

Bicornuate Uterus

Results from incomplete fusion of müllerian ducts. The two separate uterine cavities lead to the same cervix. May cause infertility, spontaneous abortion, preterm labor, and regurgitation endometriosis.

FLASH BACK

Trichomonas vaginalis is a flagellate protozoan (see Figure 9-50) that is transmitted sexually. Hence the sexual partner needs treatment with metronidazole as well.

FLASH BACK

Candida albicans is a dimorphic fungus. It demonstrates pseudohyphae, true hyphae, and budding yeasts on KOH mount.

KEY FACT

Addition of KOH to vaginal secretions is known as the **whiff test**.

KEY FACT

Clue cells are epithelial cells adherent with *Gardnerella vaginalis*.

KEY FACT

The pH of the normal vagina is below 4.5 and is maintained by the production of lactic acid. Estrogen-stimulated vaginal epithelial cells are rich in glycogen, which is broken down into glucose. The vaginal cells and lactobacilli convert glucose into lactic acid.

KEY FACT

Frequent sexual intercourse or the use of douches cause the vaginal pH to be alkaline, which predisposes to bacterial vaginosis. Semen has an alkaline pH.

INFECTIOUS DISEASES

The organisms, pathogenesis, signs and symptoms, and treatment of common infectious diseases of the vulvovaginal area are shown in Table 9-16.

Disease, organisms, signs and symptoms, and treatment of STDs presenting with genital ulcers are summarized in Table 9-17.

VAGINAL DISEASES

Condyloma Acuminatum (Genital Wart)

Occurs on the female genitalia, perineum, perianal area, and rectum. Genital warts result from HPV infection acquired during sexual intercourse. Genital warts appear as soft, tan, cauliflower-like warts. Histologically, genital warts have epidermal hyperplasia with cytoplasmic vacuolization (**koilocytosis**).

Neoplasms

Clear Cell Adenocarcinoma

Correlated with girls in their late teens whose mothers took **diethylstilbestrol** (an estrogen once believed to prevent miscarriage) during pregnancy. In one-third of the at-risk population, small glandular or microcystic inclusions appear in the vaginal mucosa (vaginal adenosis). Microscopically, malignant cells appear with clear cytoplasm.

Sarcoma Botryoides (Embryonal Rhabdomyosarcoma)

Rare (except on examination). Encountered in children younger than 5 years who present with vaginal bleeding and soft polypoid grape-like masses that protrude from the vagina. Histologically, sarcoma botryoides appears as a small, round, blue-cell tumor with skeletal muscle differentiation. It also expresses muscle-specific proteins including **desmin**.

Squamous Cell Carcinoma

The most common form of vaginal cancer. The mean age of presentation is 60 years. Squamous cell carcinoma may present with painless vaginal bleeding and discharge, commonly after intercourse.

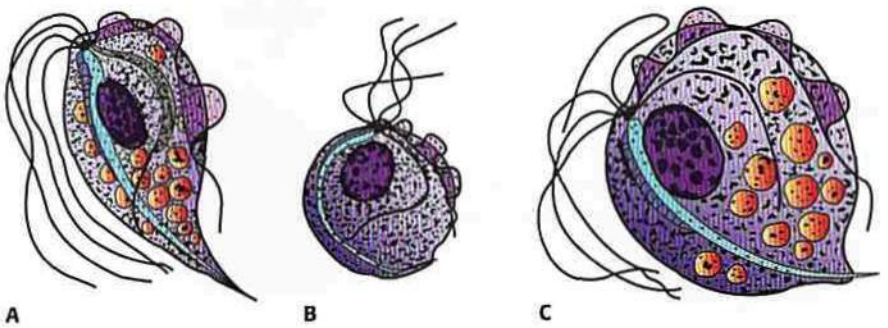


FIGURE 9-50. *Trichomonas vaginalis* as found in vaginal and prostatic secretions. (A) Normal trophozoite. (B) Round form after division. (C) Common form seen in stained preparations. (Modified, with permission, from Brooks GF, Butel JS, Morse SA, *Jawetz, Melnick, & Adelberg's Medical Microbiology*, 24th ed. New York: McGraw-Hill; 2007: 661.)

TABLE 9-16. Infectious Diseases of Vulvovaginal Area

Disease (Organism)	Pathogenesis	Signs and Symptoms	Treatment
Bacterial vaginosis (*Gardnerella vaginalis*)	Alteration of normal vaginal flora causes loss of lactobacilli and an overgrowth of predominantly anaerobic bacteria.	▪ pH > 4.5 ▪ Fishy-smelling discharge after unprotected intercourse. ▪ No inflammatory signs on examination. ▪ Clue cells on microscopy. ▪ Whiff test releases a fishy amine-like odor.	Metronidazole or clindamycin
Trichomoniasis (*Trichomonas vaginalis*)	Sexually transmitted.	▪ pH > 4.5 ▪ Purulent, thin, greenish frothy vaginal discharge associated with pruritus, dysuria, and dyspareunia. ▪ Erythema of the vulva and vagina. ▪ Punctate hemorrhages on the vagina and cervix ("strawberry cervix"). ▪ Motile trichomonads and leukocytes on microscopy ▪ Whiff test may be positive.	Metronidazole
Candidiasis (*Candida albicans*)	▪ Blastospores colonize asymptomatically. ▪ Antibiotic use, pregnancy, and diabetes predispose to symptomatic form by decreasing lactobacilli and allowing an overgrowth of fungi.	▪ pH < 4.5 (normal). ▪ Thin to homogeneously thick vaginal discharge. ▪ Vaginal soreness, pruritus, dyspareunia, and vulvar burning. ▪ Curdy white patches on the vulva and vagina. ▪ Mycelia on KOH preparation.	Topical azoles or oral fluconazole

TABLE 9-17. STDs Presenting with Genital Ulcers

Disease (Organism)	Signs and Symptoms	Treatment
Chancroid (*Haemophilus ducreyi*)	▪ Extremely painful ulcers. ▪ Tender inguinal lymphadenopathy.	Azithromycin, ceftriaxone , or erythromycin.
Genital herpes (Herpes simplex virus type 2)	Grouped small painful ulcers.	Acyclovir, famciclovir.
Lymphogranuloma venereum [inguinal bubo)] (*Chlamydia trachomatis*, serotypes D–K)	▪ Inguinal suppurative lymphadenopathy with draining sinuses. ▪ Proctitis. ▪ Rectal strictures in women and homosexuals.	Tetracycline or doxycycline; erythromycin or cotrimoxazole.
Granuloma inguinale [donovanosis] (*Calymmatobacterium granulomatis*)	Sharply demarcated ulcer with beefy-red granulation tissue.	Erythromycin or tetracycline or ampicillin.

MNEMONIC

Haemophilus "do cry" (*ducreyi*), i.e., is extremely painful.

KEY FACT

Koilocytes are cells infected with HPV. They appear to have vacuolated cytoplasm.

FLASH BACK

HPV types 16 and 18 are the subtypes causing 70% of cervical cancers.

FLASH BACK

HPV expresses E6 and E7 oncoproteins that interact with p53 and Rb, leading to malignant transformation.

KEY FACT

The most common cancer of the vagina is squamouse cell csrcinoma, followed by adenocarcinoma. Malignant melanoma is third most common cause of vaginal cancer. However, melanoma ranks **second for vulvar cancer** (squamous cell carcinoma is most common) (see Figure 9-51).



FIGURE 9-51. Vulvar cancer with fungating ulcerated growth. (Courtesy of Dr. Paban Sharma, Patan Hospital, Kathmandu, Nepal.)

The most common cancer of the vagina is squamous cell carcinoma, followed by adenocarcinoma. Malignant melanoma is the third most common cause of vaginal cancer. However, melanoma ranks **second for vulvar cancer** (squamous cell carcinoma is most common) (see Figure 9-51).

CERVICAL DISEASES

Cervical Dysplasia

Abnormal organization of cells in cervical epithelium starting from the basal layer. It has a tendency to progress from mild to severe dysplasia, and finally to invasive carcinoma. Ninety percent of cervical intraepithelial neoplasia (CIN) is associated with HPV infection. On biopsy CIN is classified as:

- CIN I (mild dysplasia): Involves the basal third of the epithelium.
- CIN II (moderate dysplasia): Involves the basal two-thirds of the epithelium.
- CIN III (severe dysplasia): Involves more than two-thirds of the epithelium.
- Carcinoma in situ: Involves the entire thickness of the epithelium.

KEY FACT

Microscopically, HPV-infected cells show cytoplasmic vacuolation (koilocytes).

KEY FACT

CIN is the histologic classification derived from biopsy, whereas ASCUS, LGSIL, or HGSIL is the cytological classification derived from Pap smear examinations.

According to the Bethesda system, atypical squamous cells are classified into those of undetermined significance (ASCUS) and those with high-grade lesions (ASC-H). Low-grade squamous intraepithelial lesion (LGSIL) includes CIN I, while high-grade squamous intraepithelial lesion (HGSIL) includes CIN II and III.

Invasive Carcinoma

Early cervical cancer is often asymptomatic. Risk factors for development include **early age at first intercourse, multiple partners, cigarette smoking, and high-risk HPV infection.**

FLASH BACK

Carcinoma in situ (biopsy) is a preinvasive neoplasm with an intact basement membrane. Dysplasia (cytological) does not necessarily progress to cancer.

KEY FACT

Most people who die of cervical cancer die from uremia secondary to the obstructive uropathy.

PRESENTATION

Post-coital vaginal bleeding, abnormal vaginal bleeding, or a mucinous discharge. In late-stage disease, the patient may present with foul-smelling vaginal discharge, weight loss, or obstructive uropathy.

HIGH-RISK HPV (TYPES 16, 18, 31, 33, 35, AND 39)

HPV infections can be detected in 85%–90% of cases. HPV types 16 and 18 integrate into the host's DNA and inactivate p53 and Rb, allowing uncontrolled cellular proliferation.

Diagnosis

Rectal examinations may reveal nodularity when carcinoma invades into the parametrium. Biopsy alone is sufficient for diagnosis.

Treatment

Cervical conization, simple hysterectomy, radical hysterectomy, or radiation therapy and chemotherapy, depending on the stage.

Prognosis

Five-year survival is above 80% with early-stage disease.

KEY FACT

The most common form of cervical cancer is squamous cell carcinoma. The second most common form is adenocarcinoma.

UTERINE DISEASES

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is infection and inflammation of the upper genital tract. Causative organisms include:

- *Neisseria gonorrhoeae.*
- *Chlamydia trachomatis.*
- Anaerobic bacteria, *Gardnerella vaginalis.*
- Less commonly *H. influenzae*, enteric gram-negative rods, and streptococci.

PID commonly occurs in young, sexually active, nulliparous women. Progestin-containing oral contraceptive pills and barrier methods may have a protective effect against PID. Risk factors include smoking, douching, and non-white race.

Presentation

Patients present with lower abdominal pain, fever with chills, and purulent cervical discharge. On examination, cervical motion tenderness (chandelier sign) and adnexal tenderness may be noted. However, many patients with PID may exhibit subtle signs and symptoms, making it difficult to diagnose.

KEY FACT

PID criteria are defined broadly in order to pick up all cases since the sequelae are so grave.

Treatment

Azithromycin and ceftriaxone are used to cover *Chlamydia* infection and gonorrhea, respectively.

Complications

Even with treatment, 25% of patients with acute PID develop recurrent PID, chronic pelvic pain, dyspareunia, ectopic pregnancy, or infertility. May also progress to Fitz-Hugh and Curtis syndrome.

KEY FACT

PID with right upper quadrant tenderness suggests associated perihepatitis from bacterial transmigration across the peritoneum. This condition is known as Fitz-Hugh and Curtis syndrome.

Endometriosis

Presence of functional endometrial tissue outside the uterus. The most common sites of implantation are the pelvic viscera (the ovaries most commonly, and the rectosigmoid pouch second most commonly) and the peritoneum (see Figure 9-52). Other sites of implantation include laparotomy scars, lungs, pleura, diaphragm, kidneys, nasal mucosa, spinal canal, stomach, and breast. Endometriosis is believed to occur in 6%–8% of women of reproductive age in the United States.

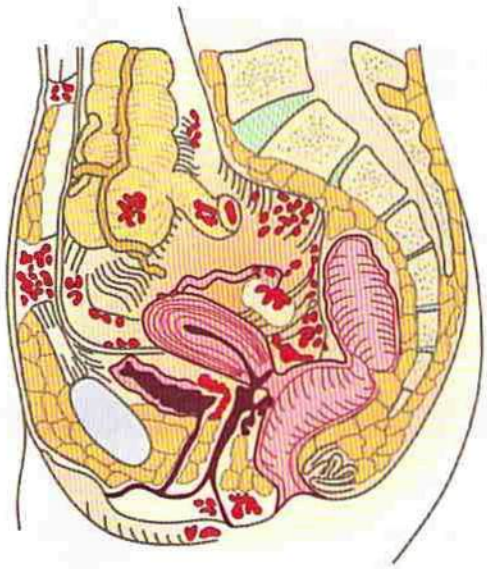


FIGURE 9-52. Endometriosis. Common sites of endometrial implants are shown.

Pathophysiology

The exact etiology of endometriosis is not known; however, there are several theories proposed to explain the occurrence of endometriosis.

- **Regurgitant flow theory (ectopic implantation and menstrual regurgitation, aka retrograde menstruation or Sampson's theory):** Menstrual regurgitation occurs in 80%–90% of women during normal menstruation. The endometrial cells get implanted and function normally as if they were in the uterine cavity.
- **Celomic metaplasia:** Conversion of one normal cell type to another (i.e., hemoptysis and epistaxis concurrent with each period point to upper respiratory endometriosis).
- **Induction theory:** Some believe that under the influence of immunologic and hormonal factors undifferentiated peritoneal cells get transformed into endometrial cells.
- **Genetic factor:** A relative risk of 7 has been shown in women who have first-degree relatives affected with endometriosis. Twin studies support the role of genetic influences.

Presentation

There are a variety of manifestations, ranging from no complaints to the following:

KEY FACT

Suspect endometriosis in women with new-onset dysmenorrhea.

- Subfertility or infertility.
- Dysmenorrhea.
- Dyspareunia.
- Chronic pelvic pain.
- Pain on defecation.
- Pain on urination.
- GI symptoms like nausea, vomiting, bloating, distention, and altered bowel habits.

The physical examination may be normal in the majority of women. However, the following findings may be present:

- Pelvic tenderness.
- Adnexal tenderness.
- Tenderness and nodularity over the uterosacral ligaments or in the posterior cul-de-sac.
- Unilateral ovarian enlargement.
- Retroverted uterus.

KEY FACT

Endometrioma is a pseudocyst formed by accumulation of menstrual debris from shedding and bleeding of the small implant over the ovarian cortex. These are also called **chocolate cysts** because of the color of fluid.

Diagnosis

- A transvaginal sonogram has excellent specificity and sensitivity in detecting ovarian endometriotic cysts.
- Laparoscopic findings of endometriosis with histologic confirmation remain the gold standard for the diagnosis of endometriosis (see Figure 9-53).
- Laparoscopic findings include typical lesions that appear to be like **powder burns**, or red implants, serous or clear vesicles, white plaques, yellow-brown discoloration of the peritoneum, and scarring. The pathologic diagnosis requires the presence of two of the following: endometrial glands, endometrial stroma, and hemosiderin-laden macrophages.

Treatment

- Progestins stop proliferation of endometrial cells by shutting down the hypothalamic-pituitary-ovarian axis, resulting in endometrial atrophy.
- Danazol is useful in endometriosis because of its anti-gonadotropin activity. Danazol directly acts on the pituitary to decrease the level of gonadotropins.
- A GnRH analogue also acts by decreasing the level of LH and FSH, thereby decreasing the estrogen level.
- The goal of **surgical management** is to preserve fertility and decrease symptomatology. The least expensive and least invasive procedures should be the preferred choices.

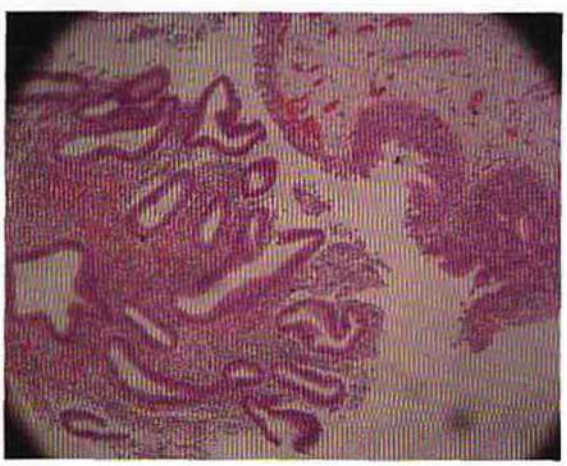


FIGURE 9-53. Endometriosis. This specimen shows endometrial glands in the urinary bladder (bladder endometriosis). (Courtesy of Dr. Paban Sharma, Patan Hospital, Kathmandu, Nepal.)

Adenomyosis

- Presence of endometrial glands and stroma in the myometrium of the uterus.
- May occur focally or diffusely.

MNEMONIC

Adenomyosis is "endometriosis stuck inside the myometrium."

Presentation

- Menorrhagia and dysmenorrhea.
- Asymptomatic in one-third of cases.
- Pelvic examination may reveal an enlarged soft, bulky uterus, a uterine mass, or uterine tenderness.

Diagnosis

- Transvaginal sonography is the initial imaging technique of choice.
- MRI is the most accurate diagnostic test for adenomyosis.

Treatment

- Hysterectomy is the only definitive treatment.

Complication

- Anemia due to menorrhagia.

NEOPLASMS

Endometrial Hyperplasia

Proliferation of endometrial glands and stroma in a greater-than-normal gland:stroma ratio. **Endometrial hyperplasia usually occurs due to prolonged unopposed action of estrogen on endometrial tissue,** like early menarche, late menopause, nulliparity, PCOS, PCOS and any other condition associated with anovulation (unopposed estrogen), granulosa cell tumor (secretes estrogen), tamoxifen (an endometrial agonist, despite being a breast estrogen-receptor antagonist), or unopposed estrogen therapy without concomitant use of a progestin.

There are different types of endometrial hyperplasia, which are described in Table 9-18.

TABLE 9-18. Types of Endometrial Hyperplasia, Cytologic Features, and Progression to Endometrial Carcinoma

Type	Cytologic Features	Progression to Endometrial Cancer
Simple	Cystic hyperplasia without atypia.	1%
Complex	Adenomatous hyperplasia without atypia.	3%–5%
Simple with atypia	Cystic hyperplasia with atypia.	8%–10%
Complex with atypia	Adenomatous hyperplasia with atypia.	29%

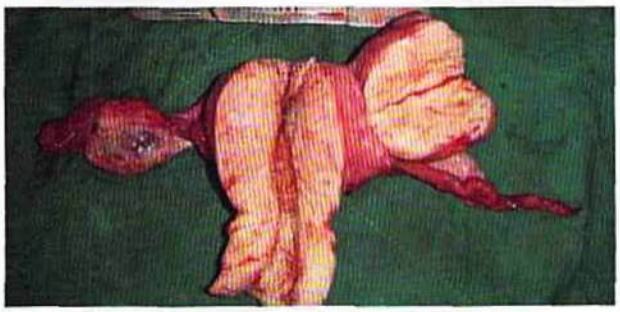


FIGURE 9-54. Subserosal leiomyoma. (Courtesy of Dr. Paban Sharma, Patan Hospital, Kathmandu, Nepal.)

Presentation

Patients with endometrial hyperplasia present with abnormal uterine bleeding, like menorrhagia, metrorrhagia, or postmenopausal bleeding. Amenorrhea may also be a presenting symptom, especially in anovulatory patients.

Diagnosis

The diagnosis is based on histologic examination of specimens obtained either from dilatation and curettage or endometrial biopsy in an office setting.

Treatment

Progesterone therapy is quite effective for hyperplasia without atypia. However, complex hyperplasia with atypia may require hysterectomy because 25% of patients with atypical hyperplasia detected on endometrial biopsy or curettage specimens are found to have well-differentiated endometrial carcinoma. Women who have not completed childbearing can be treated with progestins and followed closely to preserve fertility.

Leiomyoma

A benign tumor arising from smooth muscle and connective tissue of the uterus. Leiomyomas are clonal and arise from a singe myometrial cell; they are the most common benign uterine tumors. Leiomyomas occur in 20%–50% of women of reproductive age and may be:

- Subserosal (see Figure 9-54).
- Intramural (see Figure 9-55).
- Submucosal (see Figure 9-56).

KEY FACT

Leiomyosarcoma does not arise from leiomyoma.

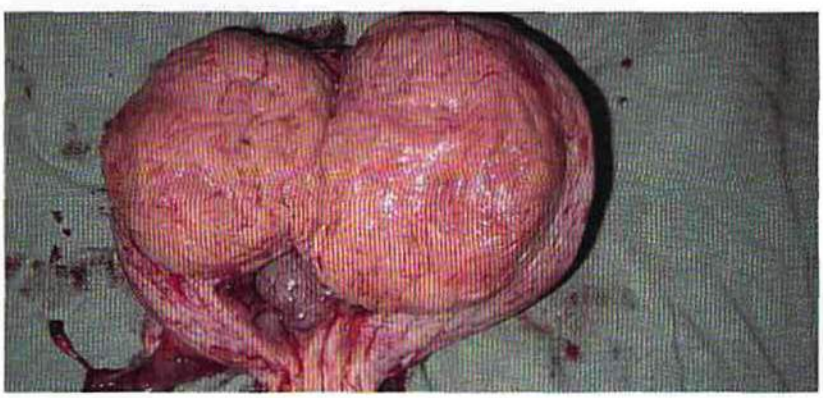


FIGURE 9-55. Intramural leiomyoma. (Courtesy of Dr. Paban Sharma, Patan Hospital, Kathmandu, Nepal.)

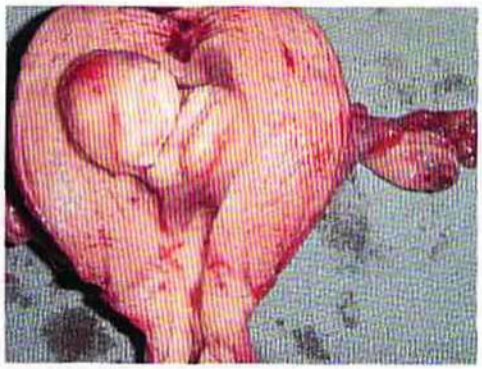


FIGURE 9-56. Submucosal leiomyoma. (Courtesy of Dr. Paban Sharma, Patan Hospital, Kathmandu, Nepal.)

Sometimes leiomyomas are found in the peritoneal cavity, broad ligament, and cervix. The exact etiology is not known. However, it is believed that leiomyomas arise from monoclonal proliferation of a single neoplastic cell within the smooth muscle of the myometrium.

Grossly, leiomyomas appear as sharply circumscribed, firm, gray-white masses with a **characteristic whorled cut surface.** Microscopically, the cells appear to be in uniform size and shape with scarce mitotic figures.

Presentation

The clinical features of leiomyoma depend on the location, size, and number of tumors. Symptoms include the following:

- Menorrhagia, which may lead to anemia.
- Pain symptoms such as dysmenorrhea, dyspareunia, or pelvic pressure. Acute pain may result from torsion of a pedunculated fibroid.
- Pressure symptoms such as frequency, urgency, incontinence, constipation, or venous stasis of the lower extremities.
- Recurrent abortions in the first trimester.
- Ascites.
- Polycythemia.

Diagnosis

Pelvic examination may reveal an asymmetrically enlarged uterus, or an adnexal or pelvic mass. Sonography shows a concentric, solid hypoechoic mass. The diagnosis is confirmed by examination of histopathology, which shows uniform-sized cells with no mitotic figures.

KEY FACT

Red degeneration is a form of coagulative necrosis in a hemorrhagic, meaty, cut surface. There are several different types of necrosis.

Treatment

- **Medical:** GnRH that acts by decreasing the level of estrogen. Long-term use of GnRH agonists is limited by their side effects such as hot flashes.
- **Surgical:** Hysterectomy or myomectomy.
- **Complications:** Calcification, ossification, mucinous or cystic degeneration, and **red degeneration;** anemia and venous stasis in the lower extremities are common complications of leiomyoma.

Endometrial Carcinoma

Cancer arising from the endometrium of the uterus. It is the most common gynecologic malignancy and 2%–3% of women develop endometrial carcinoma in their lifetime. Seventy-five percent of endometrial cancer occurs in

women older than 50 years of age. It ranks as the fourth most common malignancy in women after breast, lung, and bowel cancers. The most common risk factors for endometrial carcinoma include:

- Nulliparity
- Late menopause
- Early menarche
- Obesity
- Diabetes mellitus
- Estrogen replacement therapy
- Atypical endometrial hyperplasia
- Tamoxifen therapy for breast cancer

KEY FACT

Any factor that causes unopposed estrogen exposure to endometrium contributes to endometrial carcinoma.

Endometrial carcinoma can arise in two different pathologic settings:

- Unopposed estrogen exposure of endometrium (**hyperplastic endometrium**): In this setting, the endometrial carcinoma tends to be well differentiated with better prognosis.
- Absence of unopposed estrogen exposure of endometrium (**atrophic endometrium**): In this setting, the endometrial carcinoma tends to be less differentiated, with poorer prognosis.

KEY FACT

There is no appropriate screening test for endometrial carcinoma.

Most patients present at their perimenopausal or postmenopausal period with complaints of vaginal bleeding or discharge. The peak age of incidence is in the sixth or seventh decades of life.

Diagnosis

Endometrial aspiration biopsy is the best initial investigation of choice.

KEY FACT

Postmenopausal bleeding is endometrial carcinoma until proven otherwise.

Treatment

Total abdominal hysterectomy plus bilateral salpingo-oophorectomy with peritoneal sampling is routinely done.

Leiomyosarcoma

- Arises **from mesenchymal cells** of the myometrium, not from pre-existing leiomyomas.
- Appears similar to leiomyomas but diagnostic features include pleomorphic spindle cells **with relatively frequent mitoses**.
- Older females are affected, and pathology reveals at least 10 mitotic figures per high-power field, atypia, and necrosis.

OVARIAN DISEASES

Polycystic Ovarian Syndrome

Characterized by obesity, chronic anovulation, hirsutism, and enlarged polycystic ovaries. The most important features of polycystic ovarian syndrome (PCOS) are anovulation and signs of hyperandrogenism. Ovaries are enlarged with multiple small cysts. The cortex is thickened.

Pathogenesis

Dysregulation of the enzyme CYP-450 17α involved in androgen formation in ovaries and adrenals may be the key. This causes increased testosterone from ovarian origin. Additionally, there are elevated androgens because insulin (high here because of obesity and decreased insulin sensitivity) stimulates a decrease in sex hormone–binding globulin and an increase in testosterone. Estrogens are high due to peripheral aromatase conversion from androgens.

Additionally, estrogen inhibits FSH, so follicles do not mature or ovulate, leading to polycystic ovaries. Elevated estrogen causes positive feedback to increase LH, causing ovarian androgen secretion, inhibiting follicular maturation, and, through peripheral aromatase conversion, allowing estrogen to increase continuing the anovulatory cycle.

Insulin also suppresses the hypothalamic-pituitary axis. Some report that as many as 90% of cases of this syndrome may result from insulin resistance.

Presentation

Patients with PCOS present with hirsutism, obesity, chronic anovulation, insulin resistance, infertility, and anemia. They are also at increased risk for endometrial hyperplasia and carcinoma, possibly because of prolonged unopposed exposure to estrogen.

Diagnosis

There are three major diagnostic criteria (two of three should be met for diagnosis):

- Sonogram showing enlarged ovaries, with multiple small cysts in a "string of pearls" configuration (see Figure 9-57).
- Oligomenorrhea.
- Any form of hyperandrogenism: Clinical (acne, hirsutism) or endocrine (high levels of androgens).
- Other endocrinopathies must be ruled out, such as hypothyroidism, hyperprolactinemia, or late-onset congenital adrenal hyperplasia.

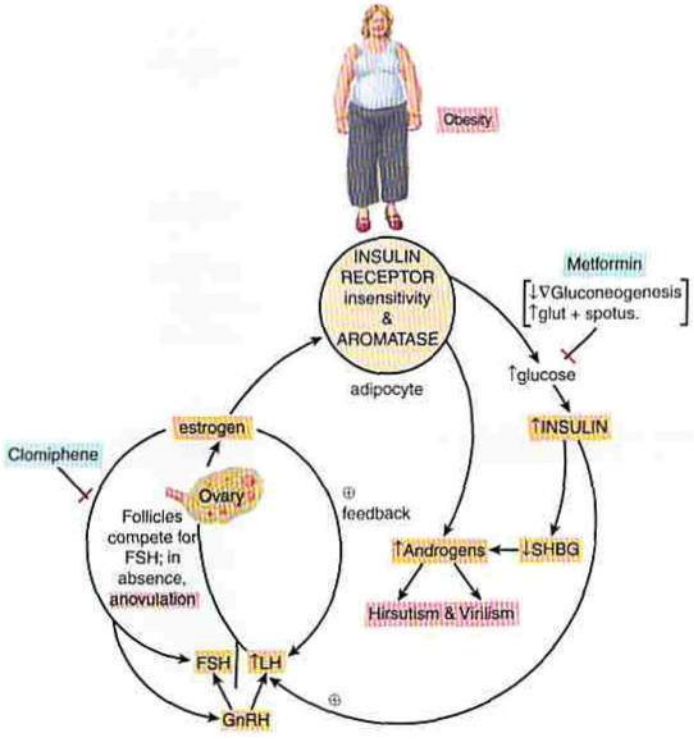


FIGURE 9-57. Different pathways contributing to the pathogenesis of PCOS.

Treatment

Weight reduction, OCPs, GnRH agonists, metformin, ketoconazole, spironolactone, clomiphene citrate, and Pergonal (menotropins) have been used with varying degrees of success.

Follicular Cyst

When the LH surge does not occur and the follicle does not extrude the ovum, it grows and results in a follicular cyst that does not usually require treatment. It goes away on its own after two or three menstrual cycles. Sometimes an OCP can be used.

Corpus Luteum Cyst

After the LH surge, the ovum is extruded. The follicle then turns into a corpus luteum. Sometimes the corpus luteum accumulates fluid, thus becoming a corpus luteum cyst. It can grow up to 6 cm in diameter and has a potential to rupture, consequently twisting the ovary. Corpus luteum cysts are also called "hemorrhagic cysts." The cysts usually regress spontaneously. There is an association of corpus luteum cysts with the use of ovulation-inducing medication such as clomiphene citrate.

KEY FACT

Hemorrhagic cysts are a common gynecologic cause of an ovarian torsion and acute abdomen in a young female.

Theca Lutein Cyst

Lined with theca interna cells, theca lutein cysts are usually bilateral and often regress spontaneously. They may grow to a large size and rupture. The cysts are associated with molar pregnancy, choriocarcinoma, twin pregnancy, Rh isoimmunization, and ovulation-inducing agents such as clomiphene citrate.

Neoplasms

Ovarian neoplasms are broadly divided into the following categories, depending on their origin:

- **Germ cell tumors**
- **Epithelial cell tumors**
- **Sex cord/stromal cell tumors**
- **Metastatic tumors**

Germ Cell Tumors

Derived from primordial germ cells of ovaries and constitute 20% of all ovarian tumors.

Presentation

Can occur at any age, but peak incidence is in the early 20s.

- About one-third of germ cell tumors diagnosed in children and adolescents are malignant, while most diagnosed in adults are benign (primarily mature cystic teratomas).
- Often present at early stages, unlike epithelial ovarian tumors, which are slow-growing and often present at late stages.
- Pelvic pain.
- Menstrual irregularities.
- Rapidly growing pelvic mass with pressure symptoms on the bladder and rectum.
- Adnexal mass, ascites, and pleural effusion may be present.

Diagnosis

Sonogram may reveal adnexal mass measuring > 2 cm with cystic or solid components.

- Karyotyping may be necessary because germ cell tumors tend to occur in dysgenetic gonads (can be seen in 46,XY females).

Types

- Dysgerminoma
- Endodermal sinus tumor
- Embryonal carcinoma
- Choriocarcinoma

Dysgerminoma

The most common malignant germ cell tumor in females. Associated with elevated **placental alkaline phosphatase (PLAP), lactate dehydrogenase (LDH), and hCG** (see Table 9-19).

- Typically unilateral, bilateral in **10%–15% cases.**
- The capsule appears thin and the cut surface is spongy and gray-brown in color (see Figure 9-58). They have large, round, ovoid, polygonal cells with clear cytoplasm and large nuclei with prominent nucleoli.
- Also seen in the presence of dysgenetic gonads and in 46,XY females.
- Highly sensitive to radiation and chemotherapy.

Endodermal Sinus Tumor

Also known as yolk sac tumor both in males and females.

- Second most common germ cell tumor of ovary; occurs in those younger than 30 years of age.
- Associated with elevated AFP levels (see Table 9-19).
- Shows glandular and papillary structures.
- Papillary structures resemble glomeruli (Schiller-Duval bodies).
- Radioresistant but chemosensitive.

TABLE 9-19. Germ Cell Tumors, Tumor Markers, and Characteristic Features

Germ Cell Tumors	Tumor Markers	Characteristic Features
Dysgerminoma	PLAP, LDH, and hCG	Large round cells with clear cytoplasm.
Endodermal sinus tumor	AFP	Blood vessels with cancer cells resembling glomeruli (Schiller-Duval bodies).
Embryonal carcinoma	hCG and AFP	Large cells, basophilic cytoplasm with indistinct borders.
Choriocarcinoma	hCG	Syncytiotrophoblast and cytotrophoblast.
Teratoma	AFP and hCG	Differentiated somatic cells from one or more germ layers.

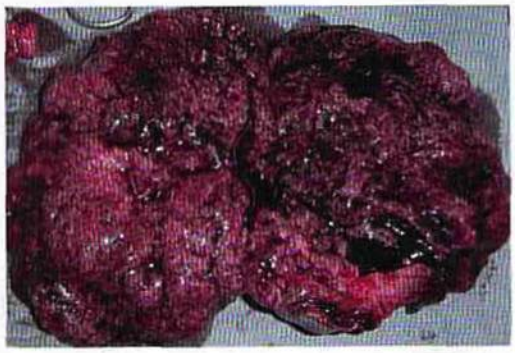


FIGURE 9-58. Dysgerminoma of ovary. (Courtesy of Dr. Paban Sharma, Patan Hospital, Kathmandu, Nepal.)

Embryonal Carcinoma

hCG and AFP **are usually elevated serum markers.**

- Appears as an ill-defined invasive mass containing foci of hemorrhage and necrosis.
- The cells are large and primitive looking, with basophilic cytoplasm, indistinct cell borders, and large nuclei with prominent nucleoli.
- May secrete estrogens, leading to precocious puberty.
- Responds to combination chemotherapy.

KEY FACT

hCG is a product of the trophoblast.

Choriocarcinoma

Grossly, primary tumors are **small, nonpalpable lesions.** Microscopically, ***cytotrophoblasts*** and ***syncytiotrophoblasts*** are seen.

- **hCG is elevated** (see Table 9-19).
- Responds well to chemotherapy; therefore, good prognosis.

KEY FACT

AFP is a product of yolk sac cells.

Teratoma

Differentiated neoplastic germ cells along somatic cell lines. They contain differentiated somatic cells fromone or more germ layers (ectoderm, mesoderm, or endoderm). Teratomas are firm masses that on cut surface often contain

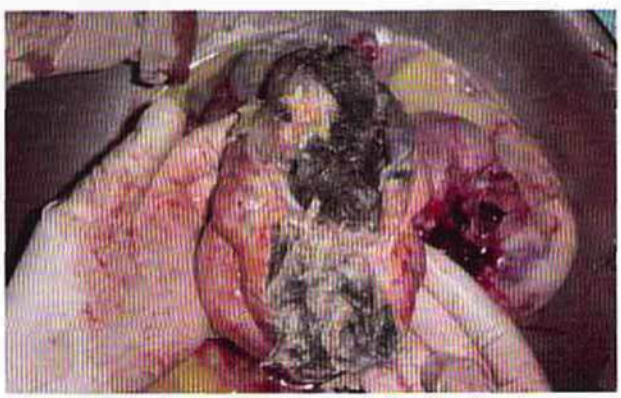


FIGURE 9-59. Cut section of mature dermoid cyst showing hairs. (Courtesy of Dr. Paban Sharma, Patan Hospital, Kathmandu, Nepal.)

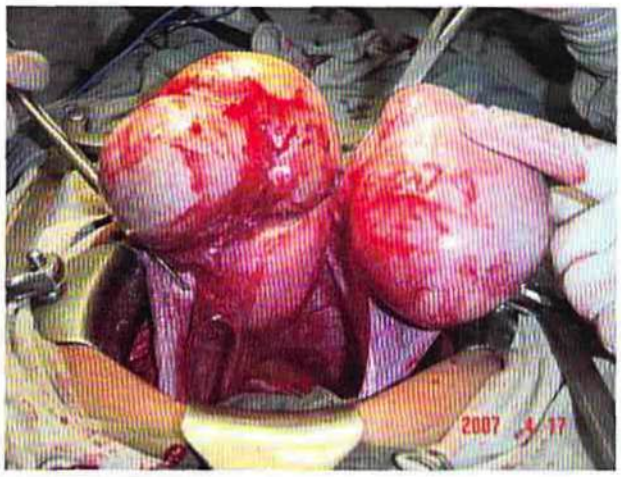


FIGURE 9-60. Intraoperative image showing bilateral immature dermoid cysts. (Courtesy of Dr. Paban Sharma, Patan Hospital, Kathmandu, Nepal.)

cysts and recognizable areas of cartilage. AFP and hCG are associated tumor markers. Histologically, there are three major variants:

- **Mature dermoid cyst:** "Dermoid" because this tumor has hair and keratin (see Figure 9-59).
  - **Benign.**
  - **Bilateral in 10%–15%** (see Figure 9-60).
  - **Most common during reproductive years.**
  - Cystic lined by epidermis and adnexal structure.
  - Contains **well-differentiated** bone, cartilage, hair, muscle, or thyroid follicles.
- **Immature dermoid cyst: Malignant**
  - Common in younger age groups.
  - Solid tumor (see Figure 9-61) with areas of hemorrhage and necrosis.
  - Contains **poorly-differentiated** elements of bone, cartilage, hair, muscle, or thyroid tissues.
  - Immature areas are always immature neuroepithelium.
- **Specialized teratoma:** Monodermal in origin
  - An example is struma ovarii, which contain only mature thyroid tissues (monodermal). Sometimes can cause hyperthyroidism (rare).

Epithelial Cell Tumors

- **Epithelial ovarian cancer:** Arises from the epithelial lining of the ovary. It usually appears at the fifth or sixth decade of life and accounts for 90% of

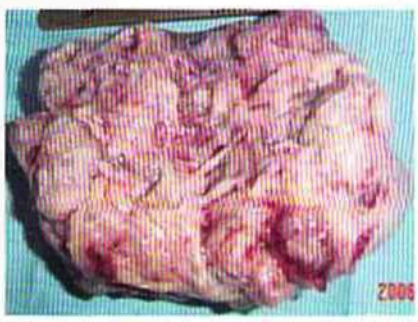


FIGURE 9-61. Immature dermoid cyst. (Courtesy of Dr. Paban Sharma, Patan Hospital, Kathmandu, Nepal.)

all ovarian cancer. Risk factors include low parity, infertility, early menarche, and late menopause. **The use of oral contraceptive pills has been documented to help prevent ovarian cancer.**

Types include:

- Serous
- Mucinous
- Brenner
- Endometrioid

Serous

Serous cystadenocarcinoma:

- Characterized by ingrowths of papillary and glandular **structures** with **stromal invasion.**
- **Psammoma bodies** are present in 80% of cases.
- **Poorly-differentiated** cancer may present as solid sheets of cells.

Serous cystadenoma:

- Filled with pale yellow serous fluid.
- Bilateral **in 10%–25% of cases.**
- Treatment is either unilateral salpingo-oophorectomy or ovarian cystectomy.

Borderline Epithelial Tumor

Characterized by **low malignant potential**. It remains confined to the ovary for a long time and has a very good prognosis. These tumors characteristically break off and transcelomically metastasize one-third of the time to other organs, most commonly the liver. The following characterize borderline epithelial tumors:

- Papillary formation and pseudostratification.
- Nuclear atypia.
- No true stromal invasion, although they are malignant in that they metastasize.

Mucinous

- **Mucinous adenocarcinoma:** Characterized by multiple loculi lined with mucin-secreting epithelium and stromal invasion.
- **Bilateral** in 8%–10% **of cases.**
- **Mucinous cystadenoma:** Filled with sticky mucin; tends to be **multiloculated.**
- Bilateral in < 5% of cases.
- Can present very large.
- Treatment is either unilateral salpingo-oophorectomy or ovarian cystectomy.

Brenner Carcinoma

- Characterized by transitional cell (bladder) epithelium with stromal invasion.
- **Rare** (except on exams).

KEY FACT

CA-125 is used to follow for recurrence and is never diagnostic!

KEY FACT

CA-125 = surface derived.

KEY FACT

Psammoma bodies are also seen in meningioma and papillary carcinoma of the thyroid.

FLASH FORWARD

Lobar carcinoma in situ is also a bilateral carcinoma.

KEY FACT

Pseudomyxoma peritonei results from slow leakage of mucin from a mucinous adenocarcinoma of the ovary.

Endometrioid Carcinoma

- Characterized by similar adenomatous pattern seen in endometrial carcinoma of the uterus.
- Often present with abdominal distention, pelvic or abdominal pain, and **abnormal vaginal bleeding.**
- Presents at early stage; therefore, has better prognosis.

KEY FACT

Endometrioid carcinoma of the ovary correlates with concurrent lesions in the endometrium.

Clear Cell Carcinoma

- Hobnail cells are clear, with nuclei projected toward apical cytoplasm.
- Associated with paraneoplastic hypercalcemia.
- Patients with clear cell carcinoma treated with platinum-based chemotherapy have a higher risk of thromboembolic complications than those with non–clear cell carcinoma.

Sex Cord/Stromal Cell Tumors

Arise from stroma or sex cords of the ovary; account for < 10% of all ovarian cancers.

FLASH BACK

Granulosa cells convert androstenedione into estrone via aromatase.

Granulosa Cell Tumors

Estrogen-secreting tumor. Granulosa cells secrete estrogen, which can be used as a tumor marker.

- In prepubertal girls, often associated with pseudo-precocious puberty.
- In reproductive age group, associated with menstrual irregularities, endometrial carcinoma (5%), and endometrial hyperplasia (50%).
- Some secrete inhibin; can be used as a tumor marker.
- Grossly, smooth with lobulated surfaces; size can range from few millimeters to 20 cm.
- Often cells arrange themselves around a central cavity like a primordial follicle (Call-Exner bodies).
- Coffee bean (grooved) nuclei are common.
- Bilateral in less than 2% of cases.

Sertoli-Leydig's Cell Tumor

Androgen-producing tumor and may contain **Reinke crystals.**

- Occur between 30 and 40 years of age.
- Because of the type of hormone produced, commonly presents with signs of virilization such as amenorrhea, breast atrophy, acne, hirsutism, deepening of the voice, and receding hairline.
- Elevated testosterone and androstenedione with normal dehydroepiandrosterone sulfate.
- Bilateral in less than 1% of cases.

Metastatic Tumors

- **Krukenberg's tumor:** Metastatic tumor to ovaries from other sites.
- Occurs in ovarian stroma.
- Cells are typically mucin-filled, with signet ring appearance.
- Usually bilateral (evidence for hemometastasis).
- Commonly metastasis occurs from stomach and less commonly from other sites such as colon, breast, or biliary tract to the ovaries.

PREGNANCY COMPLICATIONS

Placental Disorders

Abruptio Placentae

Separation of normally implanted placenta due to hemorrhage in the decidua basalis of the endometrium before the delivery of the fetus. Severe abruptions have a 25% rate of perinatal mortality.

Presentation

Vaginal bleeding, tender uterus, fetal distress, hypertonus, or stillbirth. Sometimes, the bleeding may be severe, leading to shock, and it can also lead to disseminated intravascular coagulation (DIC). The bleeding is often painful.

KEY FACT

Abruption: Painful
Previa: Painless

Diagnosis

Mainly clinical. A retroplacental clot on ultrasound is specific for abruption.

Treatment

Prompt delivery of the fetus via cesarean section. Vaginal delivery is preferred if the fetus is deceased and the mother is stable.

Placenta Accreta

Defect in the decidua basalis leading to abnormal implantation of the placenta. When Nitabuch's membrane is deficient, the trophoblastic tissue attaches directly to the myometrium. Incomplete separation of the placenta during delivery leads to profuse hemorrhage.

Presentation

Profuse placental hemorrhage during delivery.

Diagnosis

Sonography may help diagnosis in the antepartum period.

Treatment

Hysterectomy

Placenta Previa

Implantation of the placenta over or near the internal cervical os. The incidence of placenta previa is 1 in 300 deliveries in the United States.

KEY FACT

Do not perform vaginal examination in any woman who is > 20 weeks pregnant with vaginal bleeding. The digital examination may rupture the previa.

Presentation

Painless vaginal bleeding at the end of the second trimester or later. The uterus is soft and nontender.

Diagnosis

Sonography is the initial investigation of choice for localization of the placenta.

Treatment

The choice of treatment depends on gestational age, maternal and fetal conditions, and the amount of bleeding.

Expectant Management

If fetal lung maturity is not achieved, the pregnancy may be prolonged using tocolytics and dexamethasone.

Delivery

Cesarean section

Complications

Maternal: Hemorrhage, shock, and maternal death. Fetal: Prematurity and perinatal mortality.

Ectopic Pregnancy

Implantation of blastocysts outside the uterine cavity. The most common location for ectopic pregnancy is the ampulla of the fallopian tube. The rate of ectopic pregnancy is 2% of all pregnancies in the United States, with African Americans at increased risk. Risk factors include **previous tubal surgery**, **previous ectopic pregnancy**, IUD use, **PID** or previous abdominal surgery, infertility, and current smoking. A pregnancy in a patient with an IUD is more likely to be ectopic, because the chances of an intrauterine pregnancy are greatly reduced.

KEY FACT

The level of β-hCG doubles every 48 hours for an intrauterine pregnancy (a minimum of every 72 hours). In an ectopic pregnancy, the β-hCG rise is slower.

Presentation

Patient classically presents with amenorrhea, abdominal pain, vaginal bleeding, fainting, or dizziness. On examination, abdominal tenderness and cervical motion tenderness may be present, and an adnexal mass can be palpable.

Diagnosis

Urine pregnancy test, sonogram, and measurement of β-hCG are extremely sensitive diagnostic tests. Transvaginal sonography is more sensitive for a gestational sac.

FLASH BACK

MTX inhibits dihydrofolate reductase, resulting in a decrease in deoxythymidine monophosphate levels and a consequent decrease in DNA and protein synthesis.

Treatment

- **Medical**: Methotrexate (MTX) is the drug of choice for medical management. MTX is a folate antagonist that is able to kill rapidly dividing trophoblastic cells.
- **Surgical**: Laparoscopic **salpingostomy** or salpingectomy. A laparotomy approach can be used in unstable patients (see Figure 9-62).

Amniotic Fluid Disorders

Amniotic fluid is produced by the fetus, aids in normal growth and development, and helps protect the fetus. Too much (polyhydramnios) or too little (oligohydramnios) amniotic fluid can lead to abnormalities in the developing fetus.

Polyhydramnios

- May result from inability to swallow amniotic fluid.
- **Associated** with fetal intestinal atresia, esophageal/duodenal atresia, anencephaly, maternal diabetes, neural tube defects, and multiple gestations. amniotic fluid index (AFI) > 24 cm or amniotic fluid volume > 1.5–2 L.

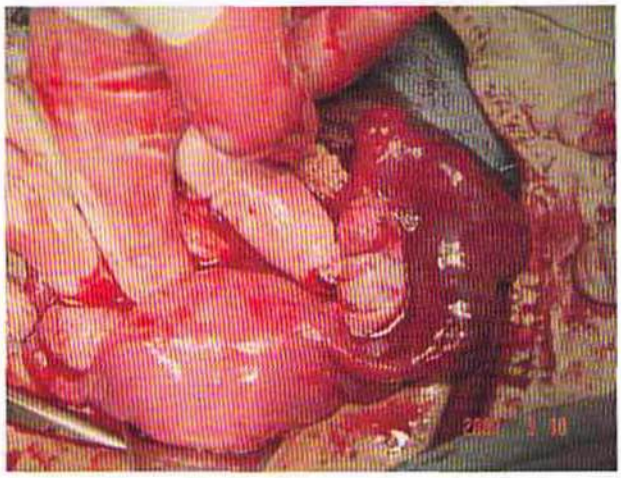


FIGURE 9-62. Intraoperative image showing ectopic pregnancy with hemoperitoneum. (Courtesy of Dr. Paban Sharma, Patan Hospital, Kathmandu, Nepal.)

OLIGOHYDRAMNIOS

- Associated with ruptured membranes, Potter's syndrome, placental insufficiency, and agenesis of posterior urethral valves (in males) and resultant inability to excrete urine.
- AFI < 5 cm or amniotic fluid volume < 0.5 L.

KEY FACT

The fetus drinks and pees amniotic fluid. Hence, if it can't drink, it gets polyhydramnios, and if it can't pee it gets oligohydramnios.

Hypertensive Disorders

PREECLAMPSIA

Defined as new-onset hypertension and proteinuria after 20 weeks of gestation. It has an incidence of 23.6 per 1000 deliveries in the United States. The criteria for preeclampsia:

- Systolic BP = 140 mmHg or diastolic BP = 90 mmHg after 20 weeks of gestation, on two readings taken 6 hours apart while the patient is on bed rest.
- Proteinuria: 0.3 g per 24 hours or more.
- With or without edema.

KEY FACT

When preeclampsia presents at < 20 weeks gestation, suspect an underlying disorder such as lupus or a gestational trophoblastic neoplasm.

SEVERE PREECLAMPSIA

Preeclampsia is considered severe if **one or more of the following** criteria is present.

- Systolic BP = 160 mmHg or diastolic = BP110 mmHg after 20 weeks of gestation measured on two readings taken 6 hours apart while the patient is on bed rest.
- Proteinuria: 5 g per 24 hours or +3 or greater on two random samples collected 4 hours apart.
- Oliguria (< 500 mL/24 h).
- Severe headache.
- Cerebral or visual disturbances.
- Pulmonary edema or cyanosis.
- Epigastric or right upper quadrant tenderness.
- Elevated liver enzymes.
- Low platelets (< 100,000/mm^3).
- Intrauterine growth restriction.
- Death resulting from cerebral hemorrhage and ARDS.

FLASH BACK

Prostacyclins and nitric oxide (potent) are vasodilators, and endothelin (potent), thromboxane A_2, and angiotensin II are vasoconstrictors.

Eclampsia

New-onset grand mal seizure in the setting of preeclampsia. The exact etiology is not known. The degree of preeclampsia depends on the level of trophoblastic invasion by the placenta. The pathologic changes lead to intense vasospasm caused by the release of various mediators like prostaglandins, and interaction among prostacyclins, nitric oxide, endothelin, and thromboxane A_2.

Presentation

High BP with proteinuria or signs of severe preeclampsia, as discussed above.

Treatment

KEY FACT

Eclamptic seizures may even occur 48 hours after delivery.

Delivery of the fetus is the definitive cure for preeclampsia. During labor and delivery, magnesium sulfate may prevent severe preeclampsia and eclampsia. Hydralazine and labetalol can be used to lower the BP. **Vaginal delivery should be attempted whenever possible, weighing possible risks and benefits.**

Gestational Hypertension

Elevated BP without proteinuria after 20 weeks of gestation and followed by disappearance within 12 weeks of delivery.

Preeclampsia Superimposed on Chronic Hypertension

Sudden or new-onset increase in proteinuria, acute increase in hypertension, or development of HELLP syndrome.

HELLP Syndrome

- Hemolysis, Elevated Liver enzymes and Low Platelets in a pregnant woman.
- Mortality rate of 7%–35%.
- Can occur during antepartum period and up to 1 week postpartum with or without superimposed preeclampsia or eclampsia.
- A positive feedback loop of endothelial damage and platelet activation, leading to release of thromboxane A_2 and serotonin, causing vasoconstriction and platelet aggregation.

Presentation

KEY FACT

Complete blood count and liver function tests should be done in any pregnant woman in the third trimester presenting with malaise.

- May present with vague complaints of malaise, epigastric pain, nausea and vomiting, and headache.
- The diagnosis is often delayed in the absence of superimposed eclampsia.
- Physical examination may reveal epigastric or right hypochondriac tenderness, edema, and hypertension with or without proteinuria.

Diagnosis

KEY FACT

Suspect HELLP syndrome in a pregnant woman with a low platelet count.

- Hemolytic anemia (microangiopathic).
- Elevated liver enzymes and low platelets.

Treatment

- The best treatment for HELLP syndrome is termination of the pregnancy. **Corticosteroids should be given to all patients with HELLP syndrome.** Severe HELLP syndrome requires immediate delivery.

Sheehan's Syndrome

- Necrosis of the pituitary gland due to postpartum hemorrhage.
- The pituitary gland is enlarged during pregnancy and sudden massive bleeding or hypovolemia may cause hypoxia, leading to pituitary necrosis.
- The anterior pituitary is more often involved than the posterior pituitary.

Presentation

- Difficulty in lactation or failure to lactate is the most common initial presentation of Sheehan's syndrome.
- Other features include oligomenorrhea or amenorrhea.
- Sometimes, if diagnosis is missed at an earlier stage, may present with features of panhypopituitarism, such as hypothyroidism, secondary adrenal insufficiency, or adrenal crisis.

Diagnosis

- Diagnosis made by features of hypopituitarism seen in a patient with a history of postpartum hemorrhage.
- Decreased levels of pituitary hormones, such as TSH, FSH, LH, and GH, followed by a decreased level of target hormones, such as thyroxine, cortisol, estrogen, and progesterone.

Treatment

- Replacement of target hormones, such as hydrocortisone, thyroxine, estrogen, and progesterone.

Amniotic Embolism

- Embolism of amniotic fluid during labor and delivery.
- High mortality rate of 80%–90%.
- Exact mechanism is not known, but inflammatory cytokines and mediators are probably involved.

Presentation

- Sudden-onset dyspnea, tachypnea, and cyanosis during or after labor and delivery.
- May also present with cardiovascular collapse, hypoxemia, seizures, DIC, and bleeding.

Diagnosis

- ABG shows severe hypoxemia.
- Prolonged bleeding times, clotting times, hypofibrinogenemia, and increased fibrin degradation products can occur in the setting of DIC.
- ECG may reveal sinus tachycardia, right ventricular strain pattern, and nonspecific ST-segment changes.

Treatment

Supportive

Prognosis

60%–80% mortality

Erythroblastosis Fetalis

- Alloimmunization because of maternal exposure to foreign fetal RBCs leads to destruction of fetal RBCs by maternal antibodies directed against them.

- There are several types of RBC alloimmunization, but the most common is Rh incompatibility (especially Rh D).
- When an Rh-negative mother gets sensitized with Rh-positive fetal RBCs, antibodies are produced.
- During a subsequent pregnancy, IgD crosses the placenta into the fetus and coats Rh-positive fetal RBCs, causing hemolysis, hydrops, and hemolytic disease of the newborn.

Presentation

- Anemia, hepatosplenomegaly, and jaundice.
- May present with edema, ascites, and pericardial and pleural effusion.
- Respiratory distress due to deficiency of surfactant, pulmonary hypoplasia, pleural effusion, and/or pericardial effusion.

Diagnosis

- Blood typing, Rh factor, and antibody screening of all pregnant patients, with paternal testing if maternal antibodies are found.

Treatment

- Rh immune globulin is given to the mother at 28 weeks of gestation, and again within 72 hours after delivery as prophylaxis.
- Routinely IgD is also given to the Rh-negative mother after abortion, D&C, amniocentesis, chorionic villus sampling, abruptio placentae, placenta previa, and ectopic pregnancy, or after any bleeding during pregnancy.

GESTATIONAL NEOPLASMS

Hydatidiform Mole

Disorder resulting from abnormal fertilization of an ovum, characterized by abnormal proliferation of trophoblastic cells. The incidence is 7–10 times higher in Southeast Asian countries compared with the Western world. Occurs in 1 of 1500 live births in the United States. Risk factor for complete mole is increased maternal age only. Increased maternal age is **not** a risk factor for incomplete mole.

KEY FACT

The amount of hCG is directly proportional to the volume of trophoblasts.

Hydatidiform mole has two different types:

- **Complete mole:** Results from fertilization of an empty ovum by the haploid sperm. The nuclear material of the haploid sperm divides and forms **diploid chromosomes (46,XX)**. Therefore, the **complete** mole is **completely** paternal in origin. Fetal parts are **completely** absent.
- **Partial mole:** Results from fertilization of a normal ovum by two sperm cells. **It has triploid sex chromosomes** (69,XXY or 69,XXX). Partial mole is both maternal and paternal in origin and contains **partial** or identifiable fetal parts.

Histologic Features

- **Complete mole: Generalized** swelling of chorionic villi (hydropic villi), **diffuse** trophoblastic hyperplasia, and **marked** trophoblastic atypia. Fetal RBCs are absent.
- **Partial mole: Focal** swelling of chorionic villi, **focal** trophoblastic hyperplasia, and **mild** trophoblastic atypia. Fetal RBCs are usually present.

Presentation

- **Complete mole:** First-trimester vaginal bleeding is the most common presentation. Additional features include excessive elevations in hCG, theca lutein cysts over 5 cm in diameter, excessive uterine size, hyperemesis gravidarum, **preeclampsia in the first trimester**, and hyperthyroidism.
- **Partial mole:** Vaginal bleeding or the features of missed or incomplete abortion are the most common presentations of partial mole. The uterus is usually small for date.

Diagnosis

- **Complete mole:** hCG is excessively elevated. Sonography is sensitive and specific, revealing a "snowstorm" pattern (see Figure 9-63). **Honeycombed uterus, appearance like a cluster of grapes on imaging, and swollen villi without fetal RBCs are other important features.**
- **Partial mole:** hCG is infrequently elevated above levels that are normal for pregnancy. Sonography shows focal cystic changes in the placenta and a ratio of transverse to anteroposterior diameter > 1.5.

Treatment

- **Suction curettage** is the method of choice for evacuation of the uterine cavity. It should be followed by curettage with a sharp curette to confirm complete evacuation of the products of conception.
- **Follow-up:** Post-evacuation molar pregnancy should be followed up with weekly hCG level titers until 3 consecutive levels are negative.

Prognosis

- With complete mole, there is an 18%–28% chance of development of post–molar gestation trophoblastic neoplasia (invasive mole and choriocarcinoma). After partial mole, is it 2%–4%.

KEY FACT

Fifty percent of gestational choriocarcinomas are derived from term pregnancies, 25% from complete moles, and 25% from spontaneous abortions or ectopic pregnancies.

Choriocarcinoma

These are aggressive, **malignant tumors** composed of cytotrophoblasts and syncytiotrophoblasts arising from gestational chorionic epithelium. They usually follow evacuation of a mole, and 2% of complete moles go on to become choriocarcinoma.

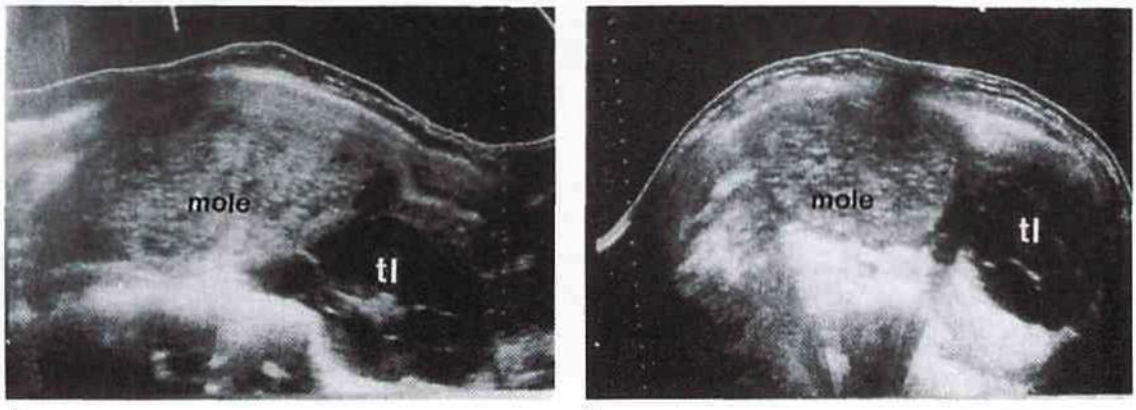


FIGURE 9-63. Hydatidiform mole. (A) Sonogram demonstrating complete mole with theca lutein cyst (tl). (B) Transverse sonogram of the same patient. (Courtesy of Dr. R. Santos as published in Cunningham FG, Leveno KL, Bloom SL, et al, *Williams Obstetrics*, 22nd ed, New York: McGraw-Hill; 2007: 278.)

Presentation

- Recurrent vaginal bleeding after evacuation of a mole or following delivery, ectopic pregnancy, or abortion. hCG levels continue to rise post-evacuation. Histologically, the cancer appears as hemorrhagic, necrotic masses within the uterus. **Chorionic villi are not present.**
- Metastases travel through the blood and seed the lung (50%), vagina (35%), liver, and brain. Chemotherapy (methotrexate) is often curative.

BREAST DISEASES

Benign Breast Disease

The female breast progresses through normal anatomic changes during pre-, peri-, and postmenopausal years. Differentiating normal from pathologic anatomic changes is important in clinical practice and in answering test questions. Keys to identifying the underlying disease process are the patient's age, history, changes related to the menstrual cycle, nipple discharge, and findings on ultrasound, mammogram, or biopsy (see Table 9-20).

Fibrocystic Change

Fibrocystic changes are common, benign changes involving the tissues of the breast that causes lumps. These changes are the consequence of exaggerated cyclic menstrual cycling, and are divided into the following:

- **Nonproliferative (cysts and fibrosis):** The most common fibrocystic change, it is characterized by an increase in fibrous stroma associated with dilation of ducts and formation of cysts of various sizes without epithelial cell hyperplasia. Calcifications will be detected on mammography.
- **Proliferative (hyperplasia and sclerosing adenosis):** The terms **epithelial hyperplasia** and **proliferative fibrocystic change** encompass a range of lesions within the ductules, terminal ducts, and sometimes lobules of the ducts. **Atypical hyperplasia is associated with the development of carcinoma,** and are estrogen-sensitive.

KEY FACT

Intraductal papilloma is the most common cause of bloody nipple discharge in women younger than 50.

Intraductal Papilloma

A neoplastic papillary growth (double-layered epithelial cells overlying a myoepithelial layer) within a duct, most often within the principal lactiferous

TABLE 9-20. Classification of Benign and Malignant Breast Diseases

Benign Breast Diseases	Breast Carcinoma
▪ Fibrocystic changes	Carcinoma in situ
▪ Intraductal papilloma	▪ Ductal
▪ Fibroadenoma	▪ Lobular
▪ Cystosarcoma phyllodes	Frank carcinoma
▪ Traumatic fat necrosis	▪ Ductal
▪ Acute mastitis	▪ Medullary
	▪ Tubular
	▪ Mucinous (colloid)
	▪ Papillary
	▪ Inflammatory
	▪ Lobular

ducts or sinuses. The presentation includes serous or bloody nipple discharge, subareolar tumors, or, rarely, nipple retraction. There may be a single papillary growth or multiple growths (more likely to be subsequently associated with carcinoma).

Acute Mastitis

Inflammation of the breast tissue caused by infection. Bacteria are the most common pathogen; fungi are rare. Staphylococcal infections can lead to abscess formation. Treatment includes antibiotics (cephalosporins, dicloxacillin) and continuation of breast feeding (if caused by milk engorgement).

KEY FACT

Staphylococcus causes localized abscess, while *Streptococcus* causes dissemination throughout the breast.

Traumatic Fat Necrosis

An uncommon and innocuous lesion significant only because it produces a mass, usually after some antecedent trauma to the breast. The lesion consists of a central focus of necrotic fat cells surrounded by PMNs; it later becomes enclosed by fibrous tissue, and then scars. **The necrotic fat is phagocytosed by macrophages, which thus become lipid-laden.** Can progress and cause skin retraction.

Fibroadenoma

This most common benign tumor of the female breast is thought to be caused by an increase in estrogen activity. Grossly, fibroadenomas are firm, with a uniform tan-white color on cut section, punctuated by softer yellow-pink specks. Clinically, they present as a **solitary, discrete, movable mass** in a young woman and rarely become malignant.

Cystosarcoma Phyllodes Tumor

Arises from the intralobular stroma and rarely from pre-existing fibroadenoma. It is the malignant counterpart of fibroadenoma. Most grow to a massive size, distending the breast. On gross section, they exhibit leaf-like clefts and slits (**phyllon** is Greek for leaf). Only about 15% are malignant and less than 20% metastasize. **There is no ductal invasion, and therefore no bleeding.**

KEY FACT

Tamoxifen acts as an antagonist in breast tissue and an agonist in endometrium and bone tissue. Raloxifene acts as an antagonist in breast tissue and an agonist in bone tissue. It has no effect on the endometrium.

Breast Cancer

Breast cancer will affect nearly one in eight females during their lifetime. Risk factors include **family history, early menarche, late menopause, late first pregnancy (after 30 years), nulliparity, never having breast-fed, previous history of breast cancer, and family history of first-degree relative with breast cancer at a young age.** Women having mutations in *BRCA1* and *BRCA2* genes have a 60%–80% chance of developing breast cancer in their lifetimes. *BRCA1* and *BRCA2* gene mutations are transmitted in autosomal dominant fashion.

Presentation

The initial chief complaint may be a palpable breast mass. Others may present with abnormal mammographic findings such as irregular masses and calcifications. The key to identifying the underlying pathology involves breast examination and tissue biopsy of the mass.

KEY FACT

The most common site for breast cancer is the upper outer quadrant, including the axilla, because lymphatics drain into this area.

Classification of Breast Cancer

Carcinoma in Situ

- **Ductal carcinoma in situ (DCIS):** Usually arises from the terminal duct lobular unit, filling and distorting involved lobules and underlying archi-

tecture, thereby appearing to involve duct-like spaces. Patients are likely to develop invasive cancer if not treated;, therefore, DCIS is considered a precursor of invasive cancer if not treated.

- **Lobular carcinoma in situ (LCIS):** Involves the terminal duct lobular unit. Signet ring cells are common. LCIS carries a 25%–35% risk of developing frank breast cancer in either breast, sometimes after a latency of up to 40 years. LCIS is considered to indicate a propensity for breast cancer rather than being a true precursor.

Frank Carcinoma

The two types are ductal and lobular.

Ductal. Term used for all carcinomas that cannot be subclassified into one of the specialized types listed below, and accounts for most breast cancers (70%–80%). It is usually associated with DCIS. Invasion of lymphovascular spaces or nerves may be seen. Roughly two-thirds express estrogen-progestin receptors and about one-third overexpress erb-B2. Types of frank ductal carcinoma include the following:

- **Medullary:** 1%–5% of all breast cancers. Occur at younger age. Although they lack estrogen and progesterone receptors, they have a better prognosis.
- **Tubular:** Presents as irregular mammographic densities. The carcinoma consists of well-formed tubules with low-grade nuclei. Affects young females. Metastases are rare, prognosis is good, and hormone receptors are normally expressed.
- **Mucinous (colloid):** Cancer cells produce mucus and grow into a jelly-like tumor; associated with a better prognosis and usually affect the elderly.
- **Papillary:** Papillary architecture and fibrovascular cores. Often expresses progesterone and estrogen receptors.
- **Inflammatory:** Presents as an enlarged, swollen, erythematous breast, usually without a palpable mass. The blockage of numerous dermal lymphatic

TABLE 9-21. Characteristics of Different Subtypes of Invasive Ductal Carcinoma

Type	Age	Pathological Findings	Prognosis
Medullary	Young	▪ Sheet-like growth with absent ducts or alveolar pattern. ▪ Estrogen/progesterone receptor absent.	Better
Tubular	Young	▪ Well-formed tubules with low-grade nuclei. ▪ Estrogen/progesterone receptor present.	Better
Mucinous	Elderly	▪ Neoplastic cells surrounded by mucin. ▪ Estrogen/progesterone receptor present.	Better
Papillary	Elderly	▪ Papillary architecture with fibrovascular cores. ▪ Estrogen/progesterone receptor present.	Better
Inflammatory	Young	▪ Swollen, erythematous base with invasion to dermal lymphatics. ▪ Estrogen/progesterone receptor present in < 50%.	Poor

spaces by carcinoma results in the clinical appearance. Most of these have distant metastases and an extremely poor prognosis.

Lobular. Often bilateral but less common than infiltrating ductal carcinoma. The cells invade individually into stroma and are often aligned in strands or chains. Lobular carcinomas, more often than ductal carcinomas, metastasize to CSF and elsewhere. Nearly all of these tumors express hormone receptors. Table 9-21 summarizes characteristics of different subtypes of invasive ductal carcinoma.

Pharmacology

DRUGS TO MODULATE GONADOTROPIN AXIS

Gonadotropin-Releasing Hormone Agonists (Buserelin, Gonadorelin)

Mechanism

Influences the anterior pituitary and secretion of FSH and LH. Synthetic GnRH is termed **gonadorelin** (see Figure 9-39). Secretion of GnRH is controlled by neural input from other parts of the brain and, through negative feedback, by sex steroids.

Uses

Pituitary function stimulation and infertility treatment. GnRH can be used to induce hypogonadism and treat prostate cancer, uterine fibroids, endometriosis, polycystic ovary syndrome, and precocious puberty.

Side Effects

Headache, light-headedness, nausea, and hypoestrogenic state; affects the cardiovascular, skeletal, and urogenital systems while producing vasomotor symptoms.

Gonadotropin-Releasing Hormone Antagonists (Danazol, Ganirelix)

Mechanism

Inhibits gonadotropin secretion and reduces estrogen synthesis.

Uses

Endometriosis, menorrhagia, and gynecomastia.

Side Effects

GI disturbances, weight gain, fluid retention, dizziness, muscle cramps, headache, and virilizing effect in females.

Gonadotropin-Modulating Agents (Leuprolide, Goserelin)

Mechanism

Acts as an agonist when used in pulsatile fashion but acts as an antagonist when used in continuous fashion. Leuprolide and goserelin are synthetic peptide analogs of GnRH. These analogs are more potent than natural hormone.

Uses

Infertility (used in pulsatile fashion). Prostate cancer and uterine fibroids (continuous; use with flutamide).

Side Effects

Antiandrogen, nausea, vomiting.

DRUGS TO MODULATE THE FEMALE REPRODUCTIVE SYSTEM

Oral Contraceptives, Combined Pills (Progesterone and Estrogen)

Mechanism

Inhibits secretion of FSH via negative feedback, suppresses development of ovarian follicles, and inhibits secretion of LH, preventing ovulation.

Uses

Contraception, reduction of endometrial/ovarian cancer risk and incidence of ectopic pregnancy, and pelvic infections.

Side Effects

Increased risk of breast cancer in women receiving hormone replacement therapy and increased triglyceride levels. Increased risk for depression, weight gain, nausea, hypertension, and hypercoagulable state. Progesterone side effects include nausea, fluid retention, and weight gain.

Trastuzumab (Herceptin)

Mechanism

Helps kill breast cancer cells that overexpress HER-2, possibly through antibody-dependent cytotoxicity. Herceptin is a monoclonal antibody against HER-2 (erb-B2).

Uses

Metastatic breast cancer.

Side Effects

Cardiotoxicity.

Mifepristone (RU-486)

Mechanism

Competitively inhibits progestins at progesterone receptors.

Uses

Pharmacologic alternative to surgical termination of pregnancy.

Side Effects

Diarrhea, pain, heavy bleeding, GI effects, nausea, vomiting, anorexia, abdominal pain.

Estrogen, Raloxifene

Mechanism

Binds to intracellular receptors and affects gene regulation. Site of action is the nucleus.

Uses

Replacement therapy as in hypo-ovarian conditions, treatment of menopause, and contraception. Raloxifene (selective estrogen receptor modulator, SERM) is used for osteoporosis.

Side Effects

Tenderness in breasts, nausea, vomiting, anorexia, salt and water retention, increased thromboembolism risk.

Clomiphene

Mechanism

Partially activates estrogen receptors in the pituitary gland. Clomiphene prevents normal feedback inhibition and increases release of LH and FSH from the pituitary, which stimulates ovulation.

Uses

Infertility treatment.

Side Effects

Increased risk of multiple pregnancies, hot flashes, ovarian enlargement, visual disturbances.

Tamoxifen

Mechanism

Upregulates transforming growth factor-β (TGF-β) a cytokine. Tamoxifen is a nonsteroidal partial agonist-inhibitor of estrogen.

Uses

Osteoporosis, estrogen-sensitive breast cancer, progesterone-resistant endometrial and ovarian cancers, melanoma and osteoporosis prevention.

Side Effects

May increase the risk of endometrial carcinoma via partial agonist effects; hot flashes.

Hydroxyprogesterone, Norethisterone

Mechanism

Forms intracellular complex, enters the nucleus and alters gene expression. Progesterone stimulates endometrial glandular secretions and spiral artery development for maintenance of pregnancy.

Uses

Hormone replacement therapy and hormonal contraception.

Side Effects

Increased BP, increased incidence of thromboembolism, weak androgenic effects, acne, fluid retention, weight change, depression, change in libido, breast discomfort, premenstrual symptoms, irregular menstrual cycles, and breakthrough bleeding.

Oxytocin, Ergometrine

Mechanism

Releases intracellular calcium stores leading to contraction of smooth muscle cells in the uterus and myoepthelial cells in the mammary gland, upon stimulation of the oxytocin receptor, which belongs to a class of G-protein-coupled receptors.

Uses

Uterine contractions. Oxytocin induces milk let-down and is also used for control of postpartum uterine hemorrhage.

Side Effects

Normal doses have few reported side effects. Reported adverse reactions are maternal deaths due to hypertensive episodes, uterine rupture, water intoxication, and fetal deaths.

Ritodrine, Salmeterol

Mechanism

Inhibits oxytocin.

Uses

Blockade of uterine contractions. These uterine relaxants are used in selected patients to prevent premature labor occurring between 22 and 33 weeks of gestation.

Side Effects

Risks to the mother, such as pulmonary edema, tremor, and arrhythmia.

Ketoconazole, Spironolactone

Mechanism

Inhibits steroid synthesis, displaces estradiol and dihydrotestosterone from sex hormone-binding protein, and increases the estradiol:testosterone ratio.

Uses

Polycystic ovarian syndrome and hirsutism. Antiandrogen.

Side Effects

Liver toxicity, which is rare but fatal. Other side effects include GI disturbances, pruritus, gynecomastia.

DRUGS TO MODULATE THE MALE REPRODUCTIVE SYSTEM

Testosterone

Mechanism

Modifies gene transcription upon conversion to dihydrotestosterone in target cells. Testosterone regulates LH production in anterior pituitary cells.

Uses

Replacement therapy in testicular failure, anemia, and as an anabolic agent.

Side Effects

Eventual decrease of gonadotropin release, with resultant infertility and salt and water retention; edema.

Finasteride

Mechanism

Inhibits the 5 α-reductase enzyme that converts testosterone to dihydrotestosterone.

Uses

Benign prostatic hyperplasia, male pattern baldness, antiandrogen.

Side Effects

Decreased libido, erectile dysfunction. Women who are or may potentially be pregnant must not use finasteride since it may cause hypospadias in a male fetus.

Flutamide

Mechanism

Inhibits androgens at the testosterone receptor.

Uses

Prostate carcinoma, hirsutism in women, antiandrogen.

Side Effects

Decreased libido, decreased volume of ejaculate, impotence, breast tenderness or enlargement.

Sildenafil, Vardenafil, Tadalafil

Mechanism

Inhibits cGMP phosphodiesterase, causing increased cGMP levels. Increased cGMP levels vasodilates vascular smooth muscle in the corpus cavernosum and increases blood flow for penile erection.

Uses

Erectile dysfunction



MNEMONIC

Sildena**fil**, vardena**fil**, and tadala**fil** **fill** the penis.

Side Effects

Headache, flushing, dyspepsia, alterations in blue-green color vision, risk of life-threatening hypotension in patients taking nitrates.

Rapid Review

Key Terms

Cryptorchidism	Failure of one or both testicles to descend from the celomic cavity into the pelvis and then the scrotum during development. Associated with fourfold increased risk of testicular cancer.
Chylocele	Lymphatic fluid within the tunica vaginalis causing scrotal enlargement.
Elephantiasis	Severe scrotum and lower extremity edema secondary to lymphatic obstruction. May be caused by filariasis.
Epididymitis	Inflammation of the epididymis, causing tenderness, groin pain, fever, and chills. Associated with UTIs/STDs.
Galactocele	A cystic dilation of an obstructed duct that arises during lactation.
Hematocele	Blood within the tunica vaginalis causing scrotal enlargement.
β-Human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP)	Tumor markers important in evaluation of germ-cell testicular cancers. Useful for monitoring persistent or recurrent tumors after therapy.
Hydrocele	Most common cause of scrotal enlargement, caused by serous fluid within the tunica vaginalis.
Orchitis	Testicular inflammation causing pain and swelling. Associated with mumps, syphilis, and UTIs, with infection ascending through the vas deferens or lymphatics of the spermatic cord to the testes.

DEVELOPMENTAL ABNORMALITIES

Bicornuate Uterus

The uterus is divided by an incomplete septum into two compartments. The vagina is normal. Caused by incomplete fusion of the paramesonephric ducts. May cause fertility issues later in life.

Hypospadias

Abnormal opening of the urethra anywhere along the ventral aspect of the penis. The urethra is often constricted, causing urinary obstruction.

Epispadias

Abnormal urethral opening on the dorsal aspect of the penis. May cause urinary obstruction due to a constricted urethra or incontinence.

SEX CHROMOSOME ABNORMALITIES

Klinefelter's Syndrome (47,XXY)

Affects 1 in 500 men. Abnormalities appear in puberty when secondary sexual characteristics fail to develop. The classic presentation is a tall male with scant body hair and gynecomastia. Due to testicular atrophy, there are low levels of testosterone and sterility is a frequent complication. Histologically, there is hyalinization of the spermatic tubules and prominent Leydig's cells.

Turner's Syndrome (45,XO)

Primary hypogonadism in phenotypic females resulting from partial or complete monosomy of the short arm of the X chromosome. Affected girls fail to develop secondary sex characteristics, the genitalia remain infantile, and little pubic hair appears. Patients are generally short with a "shield chest." Short stature and primary amenorrhea in adult patients should prompt strong suspicion. Further evaluation will show "streak ovaries." There is an association with aortic coarctation.

PROSTATIC DISEASE

The prostate can be affected by several pathologic processes: infectious, hyperplastic, or neoplastic. The typical presentation is a male > 50 years old with urinary symptoms. Age of the patient is important in determining the cause. Symptoms include pain, discomfort, or difficulty with urination, lower back pain, hematuria, or urethral discharge. Physical exam may show a tender or enlarged prostate by digital rectal exam and an elevated prostate-specific antigen (PSA).

Prostatitis

Inflammation of the prostate caused by many of the same organisms that cause UTIs. Manifestations of prostatitis include dysuria, urinary frequency, lower back pain, and poorly localized pelvic pain. May be acute or chronic as determined by microscopy.

- **Acute:** Neutrophilic infiltrate, congestion, and edema. Microabscesses may form. The prostate is often tender and boggy. Leukocytosis and fever are also seen.
- **Chronic:** Tissue destruction, increased fibroblasts, and inflammatory cells. Can be caused by recurrent UTIs or STDs.

Benign Prostatic Hypertrophy (BPH)

More common in males > 50 years old. Characterized by cellular proliferation (in the central portion) causing gland enlargement, which compresses the prostatic urethra with resultant urinary obstruction. Symptoms include urinary hesitancy, painful distention of the bladder, and hydronephrosis.

- **Dihydrotestosterone (DHT):** An androgen derived from testosterone through the action of **5 α-reductase** (pharmacologic target) that stimulates gland proliferation in patients with BPH.
- **Corpora amylacea:** Proteinaceous material trapped in the glandular lumina of the hyperplastic gland.

Prostate Cancer

Most commonly adenocarcinoma. Small glands infiltrate adjacent stroma in a haphazard pattern. Neoplastic glands lie "back-to-back" and are lined by a

single layer of cuboidal cells. Prostate cancer often develops in the periphery of the gland, causing urinary symptoms to present much later. Digital rectal exam (DRE) may show discrete nodules in the gland periphery.

- **Prostatic intraepithelial neoplasia (PIN):** Glands adjacent to areas of invasive carcinoma contain foci of epithelial atypia and may be a precancerous finding.
- **Osteoblastic metastasis:** Bone metastases are common, especially to the vertebral column. Lesions are **osteoblastic** and may cause **lower back pain.**
- **PSA:** Enzyme produced by prostatic epithelium which can be measured in the serum (normal is under 4 ng/mL). Can be elevated in BPH and cancer. Used in combination with DRE.

GESTATIONAL TROPHOBLASTIC DISEASE

Caused by abnormal fertilization. Women may present with a positive pregnancy test, vaginal bleeding, enlarged uterus, and passage of "vesicles" from the vagina. Risk factors include nullparity, smoking, and extremes of reproductive age. All produce human chorionic gonadotropin (**hCG**) at levels higher than those seen in a normal pregnancy. Serum hCG levels can be used for diagnosis and to monitor effectiveness of treatment (levels will decrease with increased effectiveness).

Hydatidiform Mole

A mass of swollen, dilated chorionic villi that grossly appear as **grape-like structures**. There are two subtypes based on abnormal fertilization.

- **Complete hydatidiform mole:** Never contains fetal parts. Villi are **hydropic** and chorionic epithelial cells are **diploid**.
- **Partial hydatidiform mole:** Compatible with early embryo formation and may contain fetal parts. Some villi are normal and almost all are **triploid**.

Invasive Mole

Complete mole that is **locally invasive** but does not have the aggressive metastatic potential of a choriocarcinoma. Retain **hydropic villi** that penetrate the uterine wall causing severe hemorrhage. Chemotherapy is curative.

Choriocarcinoma

Aggressive, **malignant tumors** composed of cytotrophoblasts and syncytiotrophoblasts arising from gestational chorionic epithelium. The tumors are hemorrhagic, necrotic masses within the uterus. **Chorionic villi are not present.** Clinically presents with bloody, brownish discharge and rising hCG titer. Metastases travel through the blood and seed the lung (50%) and vagina (35%). Chemotherapy is curative.

PREGNANCY-INDUCED HYPERTENSION

There are several physiologic changes seen in the pregnant female. BP is one parameter that can be altered to a pathologic state. Symptoms include signs of end-organ vasoconstriction: headaches, blurry vision, elevated liver function tests, edema, altered mental status, and abnormal reflexes. Severity progresses along a continuum.

Gestational Hypertension

Onset of hypertension after 20 weeks gestation without signs and symptoms of proteinuria or edema. Some patients will progress to preeclampsia.

Preeclampsia

The development of hypertension after 20 weeks gestation accompanied by proteinuria and edema.

- **HELLP syndrome:** Hemolysis, Elevated LFTs, and Low Platelets. Syndrome associated with preeclampsia.

Eclampsia

Most severe form. Symptoms of preeclampsia with convulsive seizures. May lead to disseminated intravascular coagulation (**DIC**). The cause is believed to be related to inadequate maternal blood flow to the placenta secondary to inadequate development of the spiral arteries.

COMPLICATIONS IN PREGNANCY

Abruptio Placentae

Separation of the placenta from the uterine wall. May follow a history of trauma. Associated with maternal cocaine use, cigarette smoking, and hypertension. Presents with abdominal pain and vaginal bleeding.

Placenta Accreta

Growth of the placenta into the myometrium. Prior cesarean section increases risk. Presents with abnormally heavy vaginal bleeding following childbirth.

Placenta Previa

Abnormal implantation of the placenta over the cervical os. Presents with painless vaginal bleeding.

Ectopic Pregnancy

Ectopic pregnancy is implantation of the fertilized ovum in any site other than intrauterine. Most commonly (90%), implantation is in the oviducts (**tubal pregnancy**). Indistinguishable from normal pregnancy until rupture occurs. Rupture causes intense abdominal pain followed by shock secondary to blood loss. This is a surgical emergency.

PERINATAL INFECTIONS

The fetus is vulnerable to several types of infection and can be separated by the route of infection. The infection can be ascending from the cervicovaginal canal or hematologic from the placenta. The transplacental infections can be summarized as the **TORCHES** infections.

- Toxoplasmosis
- Other infections
- Rubella
- Cytomegalovirus
- Herpes simplex/HIV
- Enteroviruses
- Syphilis

AMNIOTIC FLUID

The amniotic fluid is produced by the fetus and aids in normal growth and development, and helps to protect the fetus. Too much (polyhydramnios) or too little (oligohydramnios) amniotic fluid can lead to abnormalities in the developing fetus.

Polyhydramnios

Associated with fetal intestinal atresia, anencephaly, maternal diabetes, and multiple gestation.

Oligohydramnios

Associated with ruptured membranes, Potter's syndrome, and renal abnormalities or chromosomal abnormalities.

VAGINITIS

Inflammation of the vagina that produces a discharge (**leukorrhea**). The underlying cause can often be determined clinically by the characteristics of the discharge (appearance and odor) and microscopic analysis of the discharge (KOH and wet-prep).

Candidal Vaginitis

Produces curdy, white discharge. KOH preparation shows yeast.

Trichomonas vaginalis

Watery, copious gray-green discharge. Wet prep shows motile organisms.

Bacterial Vaginosis

Discharge is grayish with fishy odor. KOH preparation will release a strong amine odor (positive whiff test). Bacteria can be seen adherent to epithelial cells (clue cells) on a wet-prep slide.

VAGINAL CANCER

Rare. There are two scenarios with which to be familiar.

Clear Cell Adenocarcinoma of the Vagina

This develops in girls in their late teens whose mothers took **diethylstilbestrol** (an estrogen once believed to prevent miscarriage) during pregnancy. In one-third of the at-risk population, small glandular or microcystic inclusions appear in the vaginal mucosa (**vaginal adenosis**).

Sarcoma Botryoides

Rare (except on exams). Encountered in girls under 5 years who present with soft polypoid masses that protrude from the vagina.

CERVICAL PATHOLOGY

The cervix can be affected by infectious and malignant pathogens. Postcoital spotting, abnormalities of the menstrual cycle, and systemic symptoms can be

signs of cervical pathology. A pelvic exam may show masses, polyps, cysts, or inflammation.

Cervicitis

Inflammation of the cervix characterized by redness, vaginal discharge, itching, and burning. The microorganisms that cause inflammation can be infectious or non-infectious (normal flora). The most important cause of cervicitis is sexually transmitted infections, such as by *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Neisseria gonorrhoeae*, and herpes simplex virus.

Cervical Cancer

Early cervical cancer is often asymptomatic. Symptoms of postcoital vaginal bleeding, abnormal vaginal bleeding, or a mucinous discharge are usually late signs of disease. **Papanicolaou screening (Pap smear)** is a screening test that looks for abnormal cervical cells while the patient is asymptomatic. Risk factors for development include early age at first intercourse, multiple partners, and high-risk HPV infection.

- **High-risk HPV (Types 16 and 18):** HPV infections can be detected in 85%–90% of cases. HPV types 16 and 18 integrate into the host's DNA and inactivate TP53 and RB1, allowing uncontrolled cellular proliferation.

UTERINE PATHOLOGY

Clues to uterine pathology include lower abdominal pain, changes in the menstrual cycle (more or less frequent, heavier or lighter), or the range of constitutional symptoms (fever, chills, and unintentional weight loss). To determine the specific underlying cause, pay attention to the age of the patient and the characteristics of the menstrual cycle with regard to symptoms.

Endometritis

Infection of the endometrium. Frequently preceded by parturition or miscarriage and is related to retained products of conception. Presents with fever and abdominal pain in the postpartum period. Chronic endometritis can occur in association with chronic gonorrheal disease, miliary tuberculosis, IUDs, or spontaneously. Histologically, there is irregular proliferation of the glands with chronic inflammatory cells present.

Endometriosis

Foci of endometrial tissue outside of the uterus, commonly in the pelvis, peritoneal cavity, or lymph nodes. Clinically presents with dyspareunia (painful intercourse), dysmenorrhea (painful menstruation), and dyschezia (painful defecation). Patients who undergo laparoscopy may have burn lesions visualized in the pelvis. The underlying cause may be due to menstrual backflow, endometrial differentiation of celomic epithelium, or vascular/lymphatic dissemination. The histologic diagnosis of endometriosis at all sites needs two of these three elements: endometrial glands, stroma, or hemosiderin pigment.

Adenomyosis

Growth of the endometrium's basal layer into the myometrium. The uterine wall becomes thickened due to reactive hypertrophy of the myometrium. Marked involvement may produce menorrhagia, dysmenorrhea, and pelvic pain prior to menstruation, but is unusual since the **proliferating stratum basalis is nonfunctional**.

Endometrial Carcinoma

The most frequent cancer of the female genital tract, with peak incidence between 55 and 65 years old. Risk factors include obesity, diabetes, hypertension, and infertility (too much estrogen is bad). The first clinical manifestations are leukorrhea and irregular bleeding (a red flag in postmenopausal women).

- **Endometrioid:** Carcinomas frequently arise on a backdrop of endometrial hyperplasia. These tumors are termed endometrioid because they appear similar to normal endometrial glands. They originate in the mucosa and may infiltrate the myometrium and enter the vascular spaces, with metastases to regional lymph nodes.
- **Papillary serous and clear cell:** Poorly differentiated cancers that do not arise from endometrial hyperplasia and are much more aggressive tumors.

Leiomyoma (Fibroids)

The most common benign tumors that **arise from the smooth muscle cells** in the myometrium. Estrogens may stimulate growth. Sharply circumscribed, firm, gray-white masses with a **characteristic whorled cut surface**. The most common clinical manifestation is menorrhagia.

- **Intramural:** Tumors embedded within the myometrium
- **Submucosal:** Tumors directly beneath the endometrium.
- **Subserosal:** Tumors directly beneath the serosa.

Leiomyosarcoma

Arises **from mesenchymal cells** of the myometrium, not from preexisting leiomyomas. Appears similar to leiomyomas but diagnostic features include relatively frequent mitoses, with or without cellular atypia, or less numerous mitoses with cellular atypia.

POLYCYSTIC OVARIAN SYNDROME

A syndrome caused by ovulatory dysfunction and hypergonadism. Oligomenorrhea (light or infrequent menstruation), hirsutism (excessive hairiness), infertility, and obesity may appear in girls after menarche due to excessive production of androgens by multiple cystic follicles in the ovaries. The ovaries are twice normal size and studded with cortical cysts. There is cortical stromal fibrosis beneath which are innumerable cysts.

- **Luteinizing hormone (LH):** High levels are present in polycystic ovary patients.
- **Follicle-stimulating hormone (FSH):** Low levels are present in polycystic ovary patients.
- **Associations:** Type 2 diabetes and cardiovascular disease.

OVARIAN CYSTS

Common lesions that originate in unruptured follicles or follicles that rupture and quickly seal. The cysts are usually multiple, small, and filled with serous fluid. They are lined by granulosa or luteal cells. Cysts can grow large and rupture, producing intraperitoneal bleeding and abdominal pain.

Follicular Cysts

Distention of unruptured graafian follicle.

Corpus Luteum Cyst

Hemorrhage into a persistent corpus luteum.

Theca Lutein Cyst

Due to overstimulation by gonadotropins.

Chocolate Cyst

Functional endometrial tissue invades the ovaries and forms large, blood filled cysts that are called "chocolate cysts" (aged blood).

OVARIAN TUMORS

Asymptomatic until growing tumor becomes large enough to produce symptoms of abdominal distention or fullness, or a dragging sensation due to mass effect. A tumor mass also predisposes to ovarian torsion, causing intermittent intense and sharp pain. Constitutional symptoms of fever, chills, and unintentional weight loss may also be present. Several genetic markers have been associated with ovarian cancer.

- **BRCA genes (*BRCA1* and *BRCA2*):** Most hereditary ovarian cancers.
- ***ERBB2*:** Associated with a poor prognosis.
- **K-RAS:** Mucinous cystadenocarcinomas.
- ***TP53*.**
- **CA-125:** Elevated with epithelial ovarian cancer. Used to monitor response to therapy.

Serous Tumor

Large (> 30cm–40 cm), cystic tumors called cystadenomas or cystadenocarcinomas. Papillary growths project into the cystic cavities. Benign tumors are often **bilateral** and have a smooth serosal covering. When frank carcinoma develops, the cells lining the cysts (**tall columnar cells**) become anaplastic, and the tumor invades the stroma (nodular serosal covering).

- **Psammoma body:** Concentrically laminated concretions frequently found on the tips of papillae.

Mucinous Tumor

Epithelium of these tumors consists of mucin-secreting cells. Normally unilateral, multilocular lesions. Papillary formations are less common and **psammoma bodies are absent**. Most tumors are benign, with 10% being malignant **cystadenocarcinomas**.

- **Pseudomyxoma peritonei:** Mucinous deposits in the peritoneum caused by rupture of a mucinous tumor or, more commonly, a GI tumor that metastasized to the ovary ruptures.

Benign (Mature) Cystic Teratoma

These neoplasms are marked by ectodermal differentiation usually forming cysts lined by epidermis, hence the term **dermoid cyst**. They are usually found in young women and frequently contain a mix of all tissue types, including hair, teeth, and bone. Rarely do they exceed 10 cm in size. They can cause infertility and torsion.

Immature Malignant Teratoma

Average age of these patients is 18 years. These tumors are bulky, mostly solid masses with areas of necrosis. Microscopically, the distinguishing feature is a variety of barely recognizable areas of differentiation toward cartilage, bone, muscle, and nerve (bad sign).

UNIQUE OVARIAN TUMORS

Some ovarian tumors occur infrequently clinicaly, but are testable favorites. See Table 9-22.

TABLE 9-22. Ovarian Tumors

Endometrioid tumor	Malignant tumors distinguished by the formation of **tubular glands**, similar to those of the endometrium, within the linings of the cystic spaces. Associated with endometrial carcinoma.
Brenner's tumor	Uncommon tumors with abundant stroma containing nests of transitional-like epithelium resembling that of the urinary tract.
Struma ovarii	Composed of mature thyroid tissue that may hyperfunction and produce hyperthyroidism. **Stromal carcinoid** may produce carcinoid syndrome.

TESTICULAR TUMORS

Most important cause of firm, **painless, enlargement of the testis**. Virtually all arise from germ cells and are malignant. Neoplasms arising from **Sertoli's** or **Leydig's cells** are rare, but may come to attention because they can secrete steroid hormones, causing endocrine abnormalities.

- **Sertoli's cell**: Produce androgen-binding protein (ABP), in response to FSH. ABP helps maintain an androgen-rich microenvironment in the seminiferous tubules.
- **Leydig's cell (interstitial cells)**: Produce androgens in response to LH. High levels of androgens in the seminiferous tubules are essential for spermatogenesis.

Seminoma (50%)

Large, soft, well-demarcated, gray-white tumors that bulge from the cut surface of the affected testis. Confined beneath an intact tunica albuginea. Microscopically, large cells with distinct cell borders, pale nuclei, prominent nucleoli, and a sparse lymphocytic infiltrate are visible. Associated with an increase in hCG.

Embryonal Carcinoma

Ill-defined invasive masses containing foci of hemorrhage and necrosis. Metastases are common. Histologically, the cells are large and primitive looking, with basophilic cytoplasm, indistinct cell borders, and large nuclei with prominent nucleoli. The cells may be arranged in undifferentiated, solid sheets or glandular structures.

Yolk Sac Tumor (Endodermal Sinus Tumor)

Large; may be well demarcated. Microscopically, they appear as low cuboidal to columnar epithelial cells forming sheets, glands, papillae, and microcysts, often associated with **hyaline globules**. This is the most common primary testicular neoplasm in children younger than 3 years. **α-Fetoprotein (AFP)** can be demonstrated within the cytoplasm of these neoplastic cells.

- **Schiller-Duvall bodies:** Structures resembling primitive glomeruli, a distinctive feature of yolk sac tumors.

Choriocarcinoma

Tumors represent differentiation of pluripotent neoplastic germ cells along trophoblastic lines. Grossly, primary tumors are small, nonpalpable lesions. Microscopically, choriocarcinomas are composed of sheets of small cuboidal cells irregularly intermingled with or capped by large, eosinophilic syncytial cells containing multiple dark, pleomorphic nuclei; these represent **cytotrophoblastic** and **syncytiotrophoblastic** differentiation, respectively. **hCG is elevated.**

Teratoma

Differentiated neoplastic germ cells along somatic cell lines. Teratomas are firm masses that on cut surface often contain cysts and recognizable areas of cartilage. Histologically, there are three major variants.

- **Mature:** Fully differentiated tissues from one or more germ cell layers (neural tissue, cartilage, adipose, bone, epithelium) in a haphazard array.
- **Immature:** Immature somatic elements reminiscent of those in developing fetal tissue.
- **With malignant transformation:** Characterized by the development of frank malignancy in preexisting teratomatous elements, usually in the form of a squamous cell or adenocarcinoma. Usually occurs in adults.

Mixed Germ Cell Tumor

Combinations of any of the described patterns may occur in mixed tumors, the most common of which is a combination of teratoma, embryonal carcinoma, and yolk sac tumors. **hCG and AFP are elevated.**

BENIGN BREAST DISEASE

The female breast progresses through normal anatomic changes during pre-, peri-, and postmenopausal years. Distinguishing normal from pathologic anatomic changes is important in clinical practice and in answering test questions. Keys to identifying the underlying disease process is the patient's age, history, changes related to the menstrual cycle, nipple discharge, and findings on ultrasound, mammogram, or biopsy.

Fibrocystic Change

Fibrocystic changes are common and benign changes involving the tissues of the breast that cause a lump. This range of changes is the consequence of an exaggeration and distortion of the cyclic breast changes that occur normally in the menstrual cycle. It is divided into nonproliferative and proliferative changes.

Nonproliferative (Cysts and Fibrosis)

The most common type, it is characterized by an increase in fibrous stroma associated with dilation of ducts and formation of cysts of various size without epithelial cell hyperplasia. The secretions within the cysts can calcify and appear on mammograms.

- **Blue dome cyst:** The cysts vary in diameter. Unopened their color varies from brown to blue (blue dome cysts) and they are filled with serous, turbid fluid.
- **Apocrine metaplasia:** Cysts are lined by large, polygonal cells that have an abundant granular, eosinophilic cytoplasm with small, round deeply chromatic nuclei, so called apocrine metaplasia.

Proliferative (Hyperplasia and Sclerosing Adenosis)

The terms *epithelial hyperplasia* and *proliferative fibrocystic change* encompass a range of lesions within the ductules, terminal ducts, and sometimes lobules of the ducts. Atypical hyperplasia is associated with the development of carcinoma.

- **Fenestration:** Ducts, ductules, or lobules may be filled with orderly cuboidal cells, within which small gland patterns with irregular lumina at the periphery can be discerned (fenestrations).
- **Ductal papillomatosis:** Proliferating epithelium projects in multiple small papillary excrescences into the ductal lumen. Florid papillomatosis can be associated with a serous nipple discharge.

Acute Mastitis

Inflammation of the breast develops when bacteria gain access to the breast tissue through ducts, inspissation of secretions, fissures, or dermatitis involving the nipple. Staphylococcal infections can cause abscess formation with or without scarring.

Traumatic Fat Necrosis

An uncommon and innocuous lesion that is significant only because it produces a mass. It may follow some antecedent trauma to the breast. The lesion consists of a central focus of necrotic fat cells surrounded by PMNs, which later is enclosed by fibrous tissue, and then scars.

Fibroadenoma

The most common benign tumor of the female breast; it is thought to be caused by an increase in estrogen activity. Grossly, they are firm with a uniform tan-white color on cut section, punctuated by softer yellow-pink specks. Clinically, they present as solitary, discrete, movable masses and rarely become malignant.

Phyllodes Tumor

Arises from the intralobular stroma and rarely from preexisting fibroadenoma. Most grow to a massive size, distending the breast. On gross section, they exhibit leaf-like clefts and slits (**phyllodes** is Greek for leaf). Only about 15% are malignant lesions.

BREAST CANCER

Breast cancer will affect nearly 1 in 11 females during their lifetimes. Risk factors include family history, early menarche, late menopause, late first pregnancy, and previous history of breast cancer. The initial chief complaint may be a palpable breast mass, while others present with an abnormal mammographic finding. The key to identifying the underlying pathology involves breast exam and a tissue biopsy of the mass.

- **HER2/NEU protooncogene:** Overexpression of the ERBB2 (HER2/NEU) protooncogene has been found to be amplified in up to 30% of sporadic breast cancers. It is a member of the epidermal growth factor receptor family and is associated with a poor prognosis. It is believed that estrogen and progesterone receptors normally present in breast epithelium, and often present in breast cancer cells, may interact with various growth promoters to create an autocrine mechanism of tumor development.
- **Fixation/retraction (dimpling)/lymphedema/peau d'orange:** These are all common presentations of invasive cancers. Invasive carcinomas have a tendency to adhere to the chest wall, with subsequent fixation of the lesion, as well as adherence to the overlying skin, with retraction and dimpling of the skin or nipple. Involvement of the lymphatics may cause lymphedema, causing the skin to become thickened around hair follicles, a change known as peau d'orange (orange peel skin).
- **Sentinel node biopsy:** This has been introduced as an alternative, less morbid procedure to replace a full axillary dissection. The first 1–2 draining nodes are identified with a dye or radiolabel. A negative sentinel node is highly predictive of no metastatic cancer in the remaining nodes. However, the significance of finding micrometastases is unknown.
- **Trastuzumab:** The importance of evaluating ERBB2 is to predict responsiveness to a monoclonal antibody to the gene called trastuzumab. It is one of the first antitumor antibody therapies based on specific genetic abnormalities.

Intraductal Papilloma

This is a neoplastic papillary growth (double-layered epithelial cells overlying a myoepithelial layer) within a duct, most often within the principal lactiferous ducts or sinuses. They can cause serous or bloody nipple discharge, subareolar tumors, or rarely, nipple retraction. There may be a single papillary growth or multiple growths (more likely to be malignant).

Ductal Carcinoma in Situ (DCIS)

This is a noninvasive (not penetrating the limiting basement membrane) breast carcinoma that usually arises from the terminal duct lobular unit, and tends to fill, distort, and unfold involved lobules, and thus appears to involve duct-like spaces.

- **Comedo:** A subtype of DCIS that is characterized by cells with high-grade nuclei distending spaces with extensive central necrosis.
- **Paget's disease of the nipple:** This is caused by the extension of DCIS up to the lactiferous ducts and into the contiguous skin of the nipple. Clinically, there is a unilateral crusting exudate over the nipple and areolar skin. Paget's cells have an abundant clear cytoplasm.
- **Invasive (infiltrating) ductal carcinoma:** Term used for all carcinomas that cannot be subclassified into one of the specialized types listed below

and accounts for most cancers (70%–80%). It is usually associated with DCIS. Invasion of lymphovascular spaces or along nerves may be seen. About two-thirds express estrogen-progestogen receptors, and about one-third overexpress ERBB2.

Lobular Carcinoma in Situ (LCIS)

LCIS also involves the terminal duct lobular unit, is confined by a basement membrane, and usually expands but does not alter the underlying lobular architecture. It has a uniform appearance of monomorphic cells with bland, round nuclei, and occurs in incohesive clusters in ducts and lobules. Signet ring cells are common. LCIS is both a marker of increased risk of developing breast cancer in either breast, and a direct precursor of some cancers.

Inflammatory Carcinoma

Defined as the clinical presentation of an enlarged, swollen, erythematous breast, usually without a palpable mass. The blockage of numerous dermal lymphatic spaces by carcinoma results in the clinical appearance. Most of these have distant metastases and an extremely poor prognosis.

Invasive Lobular Carcinoma

The cells are morphologically the same as in LCIS. The cells invade individually into stroma and are often aligned in strands or chains. Lobular carcinomas more often than ductal carcinomas metastasize to the CSF and elsewhere. Nearly all of these tumors express hormone receptors.

Tubular Carcinoma

They usually present as irregular mammographic densities. The carcinoma consists of well-formed tubules with low-grade nuclei. Metastases are rare, prognosis is good, and hormone receptors are normally expressed.

PELVIC INFLAMMATORY DISEASE

Infection of the uterus, **fallopian tubes**, and/or the ovaries, with the tubes most commonly affected. Inflammation is almost always bacterial (*Neisseria gonorrhoeae* or *Chlamydia trachomatis*) with nongonococcal infections being more invasive. Clinically presents in young women who have unprotected intercourse and a history of STDs.

- **Symptoms:** Periodic, bilateral lower abdominal pain is the most common presentation with or without constitutional symptoms of fever and chills. Acute episodes last < 2 weeks.
- **Physical exam:** Cervical motion tenderness, cervical discharge, and pain on palpation of the adnexae.
- **Associations:** Infertility, Fitz-Hugh and Curtis syndrome (perihepatitis).

SEXUALLY TRANSMITTED DISEASES

Sexually transmitted diseases (STD) are a significant cause of morbidity with short- and long-term consequences. Table 9-23 summarizes more common STDs.

TABLE 9-23. STDs

Disease/Pathogen	Presentation	Diagnosis
Syphilis (*Treponema pallidum*)	**Primary:** Small papule that turns into a painless ulcer with well defined borders. **Secondary:** Lymphadenopathy, rash on the palms and soles of the feet, condyloma lata. **Tertiary:** Thoracic aneurysm, tabes dorsalis, gummas. **Congenital:** Stillbirth (hepatomegaly, bone abnormalities), snuffles, rash, or Hutchinson's triad (notched central incisors, interstitial keratitis [blindness], and eighth nerve palsy).	▪ Darkfield microscopy. ▪ VDRL/RPR: Measure cardiolipin antibody; titers fall after treatment. ▪ FTA-Abs: Remains positive after treatment.
Gonorrhea (*Neisseria gonorrhoeae*)	▪ Attaches to the mucosal epithelium of the urethra via pili. May ascend to infect the prostate, epididymis, or testes. ▪ Purulent urethral discharge. ▪ Swelling around the meatus. ▪ Pain with urination.	Culture of discharge will show gram-negative diplococci.
Nongonococcal urethritis (*Chlamydia trachomatis* or *Ureaplasma urealyticum*)	▪ Most common STD. ▪ Purulent urethral discharge. ▪ Pain with urination.	▪ Gram-negative intracellular organism. ▪ Reiter's syndrome: Uveitis, arthritis, urethritis.
Lymphogranuloma venereum (*C. trachomatis*)	▪ Ulcerative lesion near genitalia. ▪ Regional lymphadenopathy: Granulomatous inflammatory reaction with irregular shaped foci of necrosis and neutrophilic infiltrate.	
Chancroid (*Haemophilus ducreyi*)	▪ Tender, erythematous papule that ulcerates. ▪ Lesions are painful. ▪ Base of ulcer covered by yellow-gray exudate.	
Granuloma inguinale (donovanosis, caused by *Klebsiella granulomatis*)	▪ Papule that ulcerates with pink granulation at the ulcer base. ▪ Lymph nodes are spared. ▪ Lesion is painless.	
Condylomata acuminata (HPV types 6 and 11)	▪ Squamous cell proliferation (genital warts). ▪ Small sessile lesions to large and papillary lesions.	Koilocytosis: Hyperchromatic nuclei surrounded by a perinuclear halo.
Genital herpes (HSV types 1 and 2)	▪ Usually caused by HSV-2. ▪ Prodrome of burning and tingling. ▪ Active lesions are painful vesicles.	Microscopy: Cowdry type A inclusion bodies (viral inclusions that appear as light purple intranuclear structures surrounded by a clear halo).

NOTES

CHAPTER 10

Respiratory

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Embryology

RESPIRATORY DEVELOPMENT

The respiratory system is unique in that it is not functional during fetal life, however it must be available for immediate use after birth. Respiratory development occurs in stages in a **cranial to caudal** fashion. The upper respiratory tract (consisting of the larynx and trachea) develops first, followed by the lower respiratory tract (the bronchi and lungs). Lung development is further subdivided into pseudoglandular, canalicular, saccular, and alveolar stages which are discussed below (see Figure 10-1).

Larynx

KEY FACT

The larynx, trachea, and lung buds develop as an outpouching of the esophagus.

The larynx is a musculocartilaginous structure in the anterior neck that functions to protect the airways, aid in respiration, and produce vocalization. Its location, just below the pharynx, marks the first division between the respiratory and digestive systems. It is suspended by muscle and ligaments to the hyoid bone superiorly and attached to the trachea inferiorly.

During the third week, a small opening forms in the pharynx, the cranial part of the foregut. This opening forms the laryngeotracheal groove, which deepens to an outpouching or diverticulum. The diverticulum lengthens to form the laryngeotracheal tube, which will form the lung bud at its distal end (see Figure 10-2). The epithelium of the larynx is derived from this tube.

The laryngeal cartilage and musculature are derived from the **fourth and sixth pharyngeal arch** mesenchyme, with derivatives of the fourth arch innervated by the **superior laryngeal nerve** and derivatives of the sixth arch innervated by the **recurrent laryngeal nerve.** As the pharyngeal arches develop, a primitive laryngeal orifice, or opening, develops below the fourth arch. During week 5, swellings develop lateral to the orifice; these will become the arytenoid car-

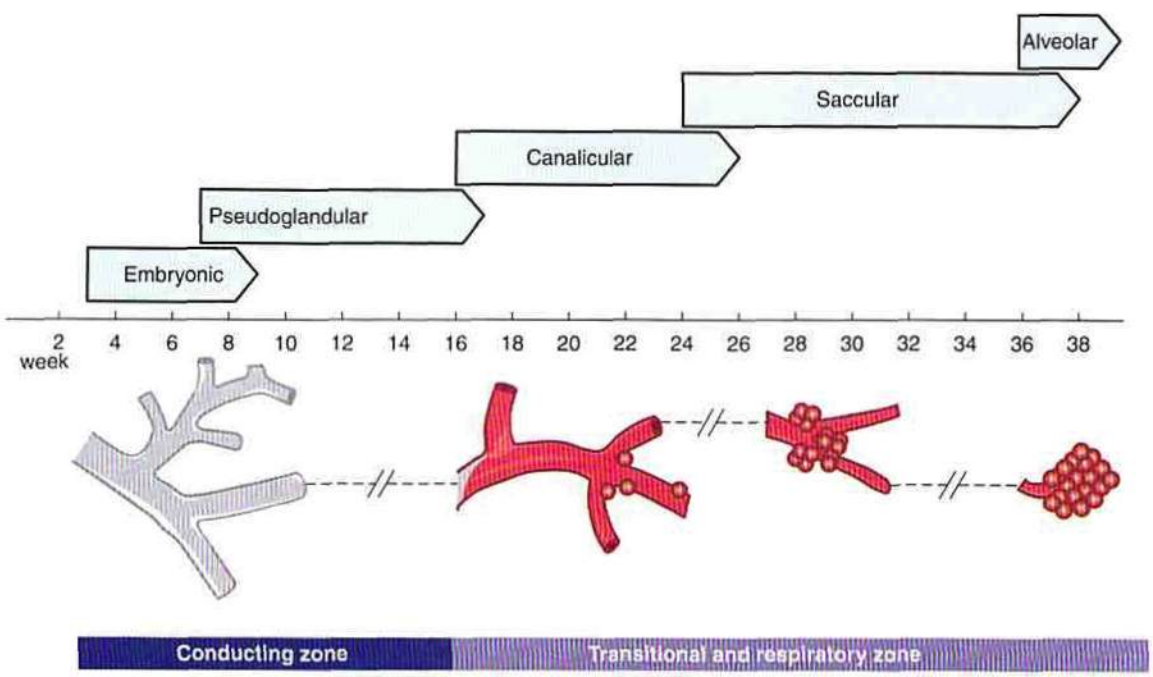


FIGURE 10-1. Overview of respiratory system development. After development of the larynx and trachea, the other conducting zones develop through branching. Subsequently the transitional and respiratory zones develop.

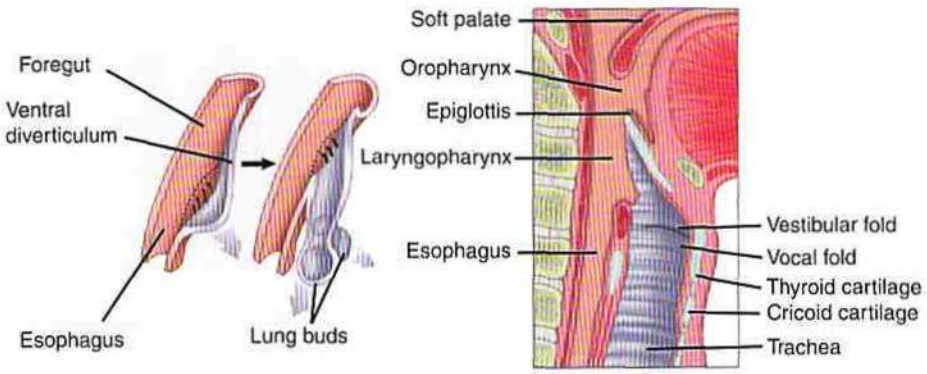


FIGURE 10-2. Larynx and trachea development. The larynx begins as a small herniation in the esophagus, known as the ventral diverticulum. As the diverticulum lengthens, lung buds form at its distal end. This will ultimately give rise to the trachea and lungs.

tilages. Additionally, an anterior swelling develops that will become the epiglottis. During week 6, continued growth in the region results in a T-shaped orifice (see Figure 10-3). Epithelial tissue occluding the opening breaks down during week 10 and surrounding epithelial tissue folds differentiate into the false and true vocal folds.

Trachea

The trachea or "windpipe" is a conducting airway that derives from the middle portion of the laryngeotracheal tube. The epithelium and glands form from the tube endoderm, while cartilage, smooth muscle, and connective tissue are derived from splanchnic mesoderm.

Bronchi

The lower laryngeotracheal tube divides into bronchi, which further divide into bronchioles (see Figure 10-4). The first asymmetric division is also accompanied by movement of the smaller **left bud** to a **more lateral position** than the larger right bud. The second division of the bronchi is also asymmetric with **two divisions occurring on the left and three divisions occurring on the right.** The tertiary bronchi continue to divide "dichotomously" until terminal bronchioles with distal extensions, the alveoli, are formed.

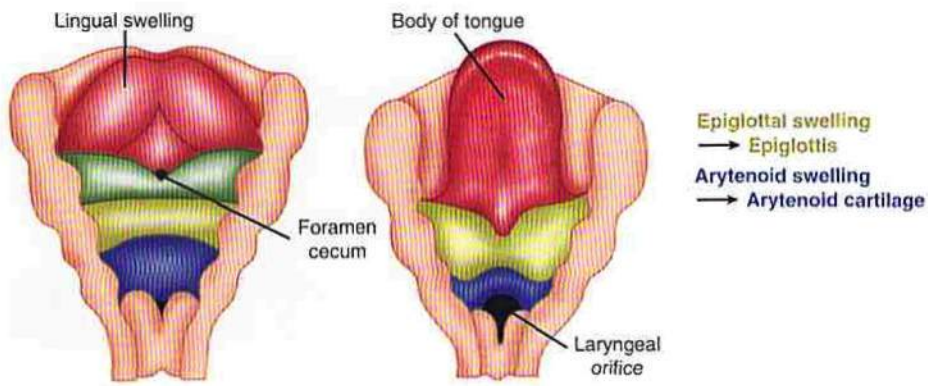


FIGURE 10-3. Larynx development from pharyngeal arches. The cartilage and musculature of the larynx are derived from the pharyngeal arches. An epiglottal swelling will give rise to the epiglottis and an arytenoid swelling will give rise to the arytenoid cartilages.

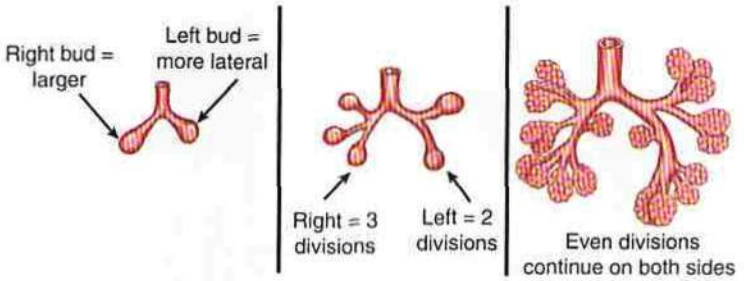


FIGURE 10-4. Bronchiole divisions. The initial two divisions of the trachea are asymmetric. During the first division, the smaller left lung bud becomes more lateral. During the second division, the larger right lung bud divides three times, while the left bud divides only twice. All subsequent divisions on both sides result in two branches.

Lungs

At the end of the fourth week, the laryngeotracheal diverticulum forms the lung buds as two lateral outpouchings. The timeline of lung development can determine the survival of premature infants:

- The lung bud forms the trachea and two bronchial buds, which will develop into bronchi and the bronchial tree during months 2 through 7 of gestation.
- The primitive alveoli begin to form during week 26.
- The number of alveolar terminal sacs continues to increase in months 8 and 9 of prenatal life and during early postnatal life.
- The amount of surfactant increases, particularly during the last two weeks of gestation.

Pseudoglandular Period (Weeks 5–16)

During this period, **branching** continues and all major parts of the lung are formed with the exception of the gas exchange elements. Without the ability to participate in gas exchange, the fetus is not viable.

Canalicular Period (Weeks 16–26)

During the canalicular period, the **airways increase in diameter** and **lung vasculature** develops (see Figure 10-5). **Primitive end respiratory units** consisting of a respiratory bronchiole, alveolar duct, and terminal sac are formed during this period.

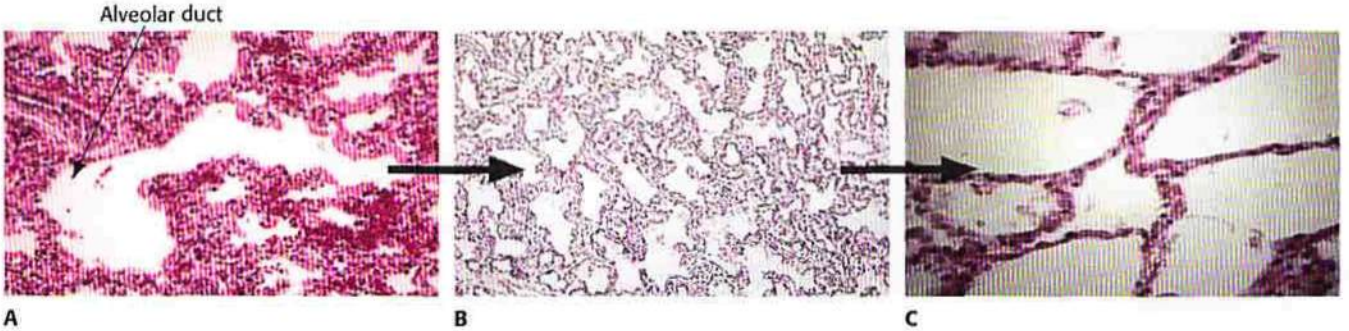


FIGURE 10-5. Canalicular, terminal sac, and alveolar periods of lung development. As the lung progresses through its developmental periods, it becomes more specialized to the job of gaseous exchange. (A) Canalicular period (16–26 weeks), increase airway diameter, respiratory bronchiole formation, alveolar duct formation, terminal sac formation. (B) Terminal sac period (26 weeks–birth), terminal sac development with thinning of the epithelial lining, appearance of type I and type II pneumocytes, capillary contact formation. (C) Alveolar period (prenatal–childhood), capillary contact development, increase alveoli number and size. (Histology images courtesy of PEIR Digital Library [http://peir.net].)

Terminal Sac Period (Week 26–Birth)

Terminal sacs develop with the **thinning of the epithelial** lining. Type I squamous epithelial cells form the gas exchange surface, while type II secretory pneumocytes, which appear later, produce surfactant.

Alveolar Period (Prenatal–Childhood)

Clusters of primitive alveoli form, allowing "breathing" in utero by aspiration of amniotic fluid. The fluid in the lungs keeps the pulmonary vascular resistance high through gestation. At birth, the lungs are half-filled with liquid that must be emptied through the mouth or absorbed into the blood and lymph. The replacement of fluid with air results in a dramatic fall in pulmonary vascular resistance at birth. The alveoli continue to mature after birth, growing in number only for the first 3 years and then increasing in both number and size for the next 5 years.

Pleural Cavities

The lungs invaginate to penetrate part of the intra-embryonic coelom, or body cavity, as they grow and branch. This leaves a layer of **visceral pleura** from the splanchnic mesoderm covering the lung, and a layer of **parietal pleura** from the somatic mesoderm covering the body wall (see Figure 10-6).

Diaphragm

The diaphragm develops more superiorly than its postnatal location but maintains its innervation from cervical roots C3, C4, and C5. It is formed from four embryologic structures that fuse by week seven of gestation:

- The **septum transversum** is formed by mesodermal tissue that projects from the ventral body wall to partially separate the thoracic cavity and abdominal cavity. In the adult, the septum transversum forms the **central tendon** of the diaphragm.
- The **pleuroperitoneal folds** extend from the dorsolateral sides of the body wall to fuse with the septum transversum.
- The **body wall** also extends from the dorsal and lateral sides (after the pleuoperitoneal folds have closed the thoracic cavity) to form the peripheral, muscular portion of the adult diaphragm.
- The **dorsal mesentery of the esophagus** forms the diaphragmatic portion that is dorsal to the esophagus and ventral to the aorta.

KEY FACT

To understand pleural cavity formation, imagine pushing your hand into an inflated balloon. The balloon represents the lining of the body cavity. The part of the balloon surrounding your fingers represents the visceral pleura, and the part of the balloon wall opposite your fingers represents the parietal pleura. The space that still contains air within the balloon represents the pleural cavity. The pressure within the pleural cavity is negative.

Visceral = organ side
Parietal = wall side

CLINICAL CORRELATION

A pneumothorax occurs when air enters the pleural cavity. The corresponding lung collapses and is unable to participate in gas exchange.

MNEMONIC

Several **P**arts **B**uild a **D**iaphragm:
Septum transversum,
Pleuroperitoneal folds, **B**ody wall,
Dorsal mesentery of the esophagus

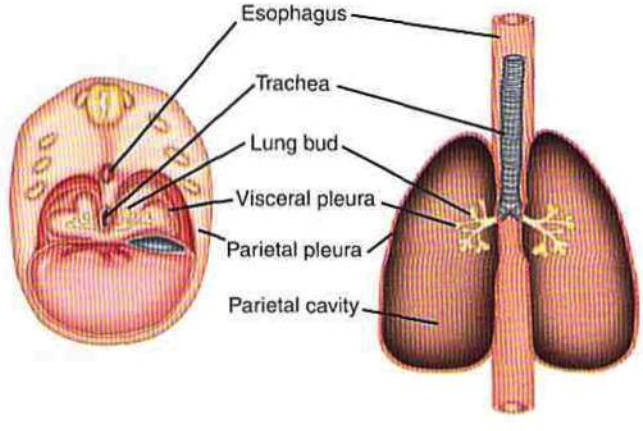


FIGURE 10-6. Pleural cavity development. The pleural cavity develops when the lung penetrates the body cavity. While some of the lining, the visceral pleura, becomes attached to the lung, the rest, the parietal pleura, remains attached to the body wall.

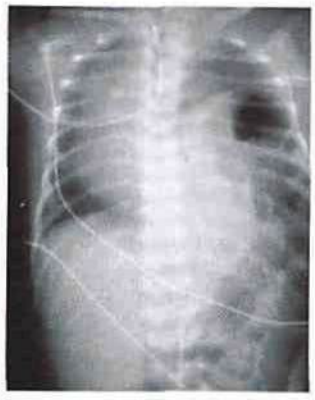


FIGURE 10-7. Congenital diaphragmatic hernia. Note the air-filled bowel in the left thoracic cavity. (Image courtesy of PEIR Digital Library [http://peir.net].)

A **congenital diaphragmatic hernia** may result if the four embryonic parts do not properly fuse. The newborn will present with respiratory distress, and a chest radiograph will show abdominal contents (loops of bowel) within the thoracic cavity (see Figure 10-7). Additionally, bowel sounds may be heard while listening over the chest.

CONGENITAL MALFORMATIONS

Esophageal Atresia

The ventral laryngotracheal diverticulum is separated from the dorsal gut tube (the esophagus at this region) by the **tracheoesophageal septum** (mesoderm). An **esophageal closure** can form as a result of posterior deviation of the tracheoesophageal septum (see Figure 10-8). In the embryo, this results in the inability to swallow amniotic fluid, leading to fluid accumulation and an enlarged uterus. In the newborn, this process causes fluid to overflow into the trachea during feedings, leading to **aspiration pneumonia.**

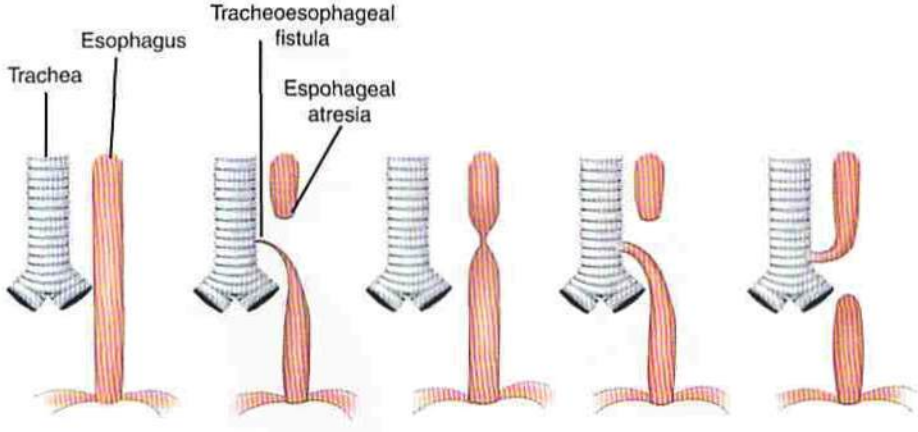


FIGURE 10-8. Congenital malformations of the trachea and esophagus. The most common congenital malformation of the trachea and esophagus is an esophageal atresia with a tracheoesophageal fistula. Less common variants include esophageal atresia alone or with other abnormal connections to the trachea.

Tracheoesophageal Fistula

As described above, the **tracheoesophageal septum** separates the developing lungs from the foregut. When the tracheoesophageal septum does not form properly, a congenital **tracheoesophageal fistula** may result. This abnormal connection between the trachea (just above the bifurcation) and distal esophagus is usually seen in association with **esophageal atresia** (see Figure 10-8). An infant with such a defect will cough upon feeding, as acidic gastric contents pass into the lung, causing severe **chemical pneumonitis**. In addition, passage of air into the stomach causes gastric dilation, elevation of the diaphragm, and impaired breathing. Air may be seen in the stomach on a chest radiograph.

Congenital Cysts

These saccular enlargements of the terminal bronchiole are usually solitary and may cause chronic infection secondary to poor drainage.

Hypoplasia

Alveolar development can fail despite normal bronchus formation (see Figure 10-9). The resulting hypoplasia of the lung is the **most common cause of diaphragmatic hernia.**

Respiratory Distress Syndrome (RDS)

During weeks 25–28, type II pneumocytes begin to produce surfactant, a phospholipid fluid that facilitates alveolar opening by reducing surface tension. If the fetus is delivered before 25 weeks of gestation, it will not be viable. Between this time and full development, the newborn is **unable to fully inflate the lungs,** leading to formation of hyaline membranes in the pulmonary alveoli (see Figure 10-10). Clinically the infant exhibits superficial, rapid breathing (**tachypnea**) and **cyanosis.** The incidence of RDS is inversely related to gestational age at birth. Current treatments include maternal steroids and surfactant replacement.

CLINICAL CORRELATION

The aspiration of amniotic fluid is essential for lung development, and fetal breathing movements are important for developing respiratory muscles. **Pulmonary hypoplasia** may result from **oligohydramnios** (too little amniotic fluid); this may be a result of renal malformation in **Potter's syndrome**.

KEY FACT

Fetal lung maturity is determined by a lecithin:sphingomyelin ratio > 2.0 in amniotic fluid.

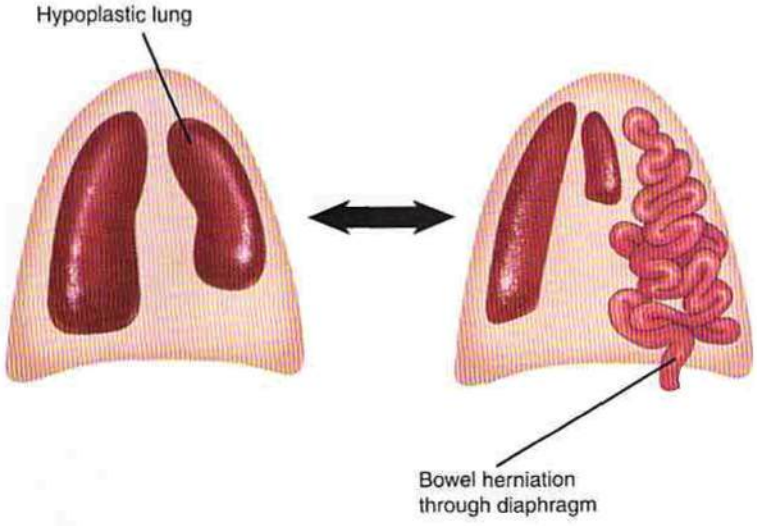


FIGURE 10-9. Lung hypoplasia. In addition to the respiratory complications from decreased gas exchange, lung hypoplasia is the most common cause of bowel herniation through the diaphragm.

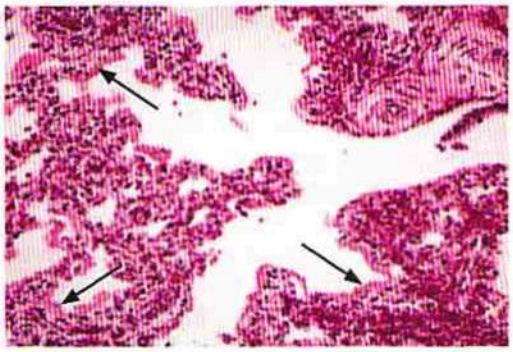


FIGURE 10-10. Hyaline membranes in an immature lung. Hyaline membranes (arrows) are made of a waxy substance consisting of fibrinous exudates and cellular debris lining the alveolar walls. (Image courtesy of PEIR Digital Library [http://peir.net].)

CLINICAL CORRELATION

Obstructive sleep apnea occurs when excess body weight or pharyngeal tissue blocks the upper airway passages when the patient is supine. This obstruction causes periods of hypoventilation and hypoxia, resulting in nocturnal awakenings, poor sleep, and daytime somnolence. Sleeping partners often complain about the patient's snoring.

FLASH BACK

The conducting airways contain a surrounding smooth muscle layer that hypertrophies and undergoes spastic constrictions in **bronchial asthma**, an obstructive lung disease.

Anatomy

The respiratory system consists of the nasal passages and mouth, pharynx, trachea, bronchi, bronchioles, lungs, and the muscles that control respiration, as shown in Figure 10-11.

AIRWAYS

The passages that transmit air from the environment to the lungs can be divided into conducting airways and respiratory airways, as described in Table 10-1.

LUNGS

The right and left lungs are structurally distinct, as described in Table 10-2.

Blood Supply of the Lungs

- The right and left **pulmonary arteries** transport relatively deoxygenated blood from the right ventricle to the lungs.

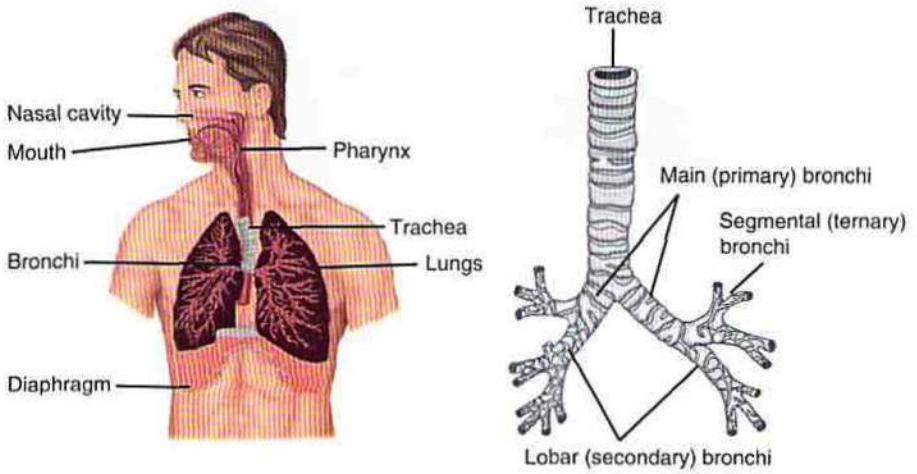


FIGURE 10-11. Gross anatomy of the respiratory system. Overview and conducting airways.

TABLE 10-1. Conducting and Respiratory Airways

	Conducting Airways	Respiratory Airways
Function	Warm, humidify, and filter air; no gas exchange (anatomic dead space)	Gas exchange
Structures	Nose/mouth, pharynx *Trachea* Bronchi Bronchioles Terminal bronchioles	Respiratory bronchioles *Alveolar ducts* Alveoli

- The **bronchial arteries** branch from the aorta to supply the bronchi and pulmonary connective tissues with nourishing, O_2-rich blood.
- Branches of the pulmonary and bronchial arteries enter the **bronchopulmonary segments** centrally alongside the **segmental (tertiary) bronchi** (see Figure 10-12).
- The **bronchial veins** drain blood supplied by the bronchial arteries; the small bronchial veins unite to form a single vessel that empties into the **azygos vein** on the right and the **hemiazygos vein** on the left.
- The **pulmonary veins** transport oxygenated blood from the alveoli to the left atrium.

The relationship among the conducting airways, respiratory airways, and blood supply to the alveoli is shown in Figure 10-12.

MNEMONIC

Right pulmonary artery is **A**nterior, **L**eft artery is **S**uperior to the bronchi: **RALS**.

KEY FACT

The visceral pleura lacks sensory innervation; however, the parietal pleura is innervated by branches of the intercostal and phrenic nerves. Thus, the parietal pleura is highly sensitive to pain, but the visceral pleura is not.

Pleura

The lungs are located within a bilayered pleural sac in the thoracic cavity.

- The **visceral pleura**, or **pulmonary pleura**, is tightly adherent to the outer surface of the lungs.
- The **parietal pleura** covers the inside of the thoracic cavity, including the diaphragm, costal walls, and the mediastinum.
- The **pleural reflections** are formed when the parietal pleura lining one surface becomes continuous with the pleura lining another surface. For example, the costal pleura is continuous with the diaphragmatic pleura, forming the costal line of pleural reflection.

MNEMONIC

The **P**arietal pleura feels **P**ain.

TABLE 10-2. Anatomy of the Right and Left Lungs

	Right	Left
Lobes	Three (upper, middle, and lower)	Two (upper with lingula, and lower)
Main bronchus entry	Lesser angle	Acute angle
Main bronchus shape	Shorter and wider	Longer and narrower
Pulmonary artery entry	Anterior to right mainstem bronchus	Superior to left mainstem bronchus

KEY FACT

An aspirated foreign object is more likely to lodge in the right mainstem bronchus, due to its lesser angle of entry and wider diameter (see Figure 10-12).

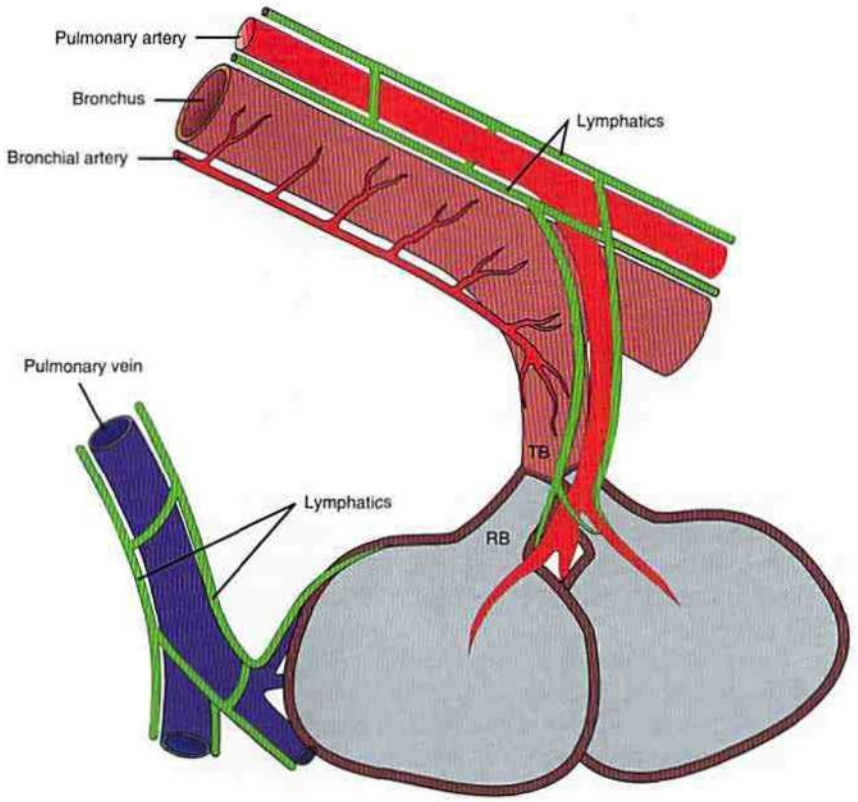


FIGURE 10-12. Anatomy of the bronchopulmonary segments. Each lung is divided into 10 functional bronchopulmonary segments, each supplied by its own artery and segmental bronchus. The pulmonary and bronchial arteries approach the alveoli alongside the bronchi, while the pulmonary vein drains blood separately. A = Alveoli; AD = alveolar duct; RB = respiratory bronchiole; TB = terminal bronchiole.

FLASH BACK

Pleural effusions have multiple possible etiologies, including infection, heart failure, trauma, and lung cancer.

Between the visceral and parietal pleura is a potential space, the **pleural cavity**, which normally contains < 10 mL of circulating fluid. In some disease states, fluid accumulates in the pleural cavity, forming a **pleural effusion**. When the patient is erect, the fluid fills the **costodiaphragmatic recess** located at the inferior part of the thoracic cavity. On a chest radiograph, the costodiaphragmatic angles are normally sharp and unoccupied by tissue or fluid, but pleural effusions blunt these angles, as seen in Figure 10-13.

DIAPHRAGM

FLASH BACK

The right **crus** of the diaphragm wraps around the esophagus to prevent **hiatal hernias,** in which the stomach slides into the thoracic cavity.

The thoracic diaphragm is a domed, musculotendinous structure that forms the inferior border of the thoracic cavity. During inspiration, the central part of the diaphragm descends, decreasing intrathoracic pressure and increasing lung volume. The peripheral parts of the diaphragm are fused to the thoracic wall and are thus immobile.

The diaphragm is a useful landmark in radiographs, as six structures penetrate it at specific vertebral levels. These structures are identified in Figure 10-14.

The inferior vena cava, aorta, azygos vein, thoracic duct, and esophagus all provide a means of transmitting blood, lymph, or food products from the thoracic cavity to the abdomen, or vice versa. The **vagus nerve** provides parasym-

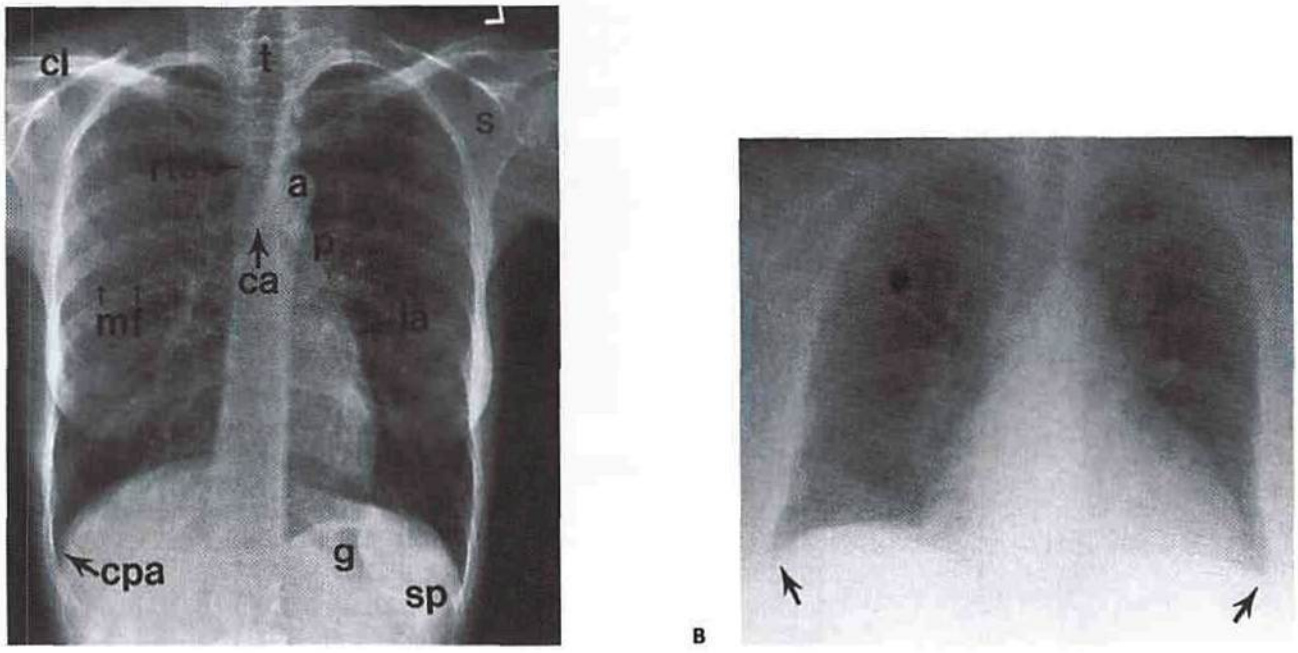


FIGURE 10-13. Chest radiographs. (A) Normal chest radiograph. (B) Chest radiograph of pleural effusion. Note the sharp costodiaphragmatic angles in the normal radiograph and blunting of the angles in a pleural effusion. (Key a = aorta, ca = carina, cpa = costophrenic angle, cl = clavicle, g = gastric air bubble, la = left atrium, mf = minor fissure, p = main pulmonary artery, rts = right tracheal [or paratracheal] stripe, s = scapula, sp = spleen, and t = trachea.) (Reproduced, with permission, from Chen MYM, Pope TL Jr, Ott DJ, *Basic Radiology*, New York: McGraw-Hill, 2004: 63, 112.)

pathetic stimulation to the heart and lungs in the thoracic cavity and then crosses the diaphragm to provide parasympathetic stimulation to the abdominal viscera.

MNEMONIC

I 8 10 **EGG**s **AAT** 12 ("I ate ten eggs at twelve").
Inferior vena cava: T8
Esopha**G**us, va**G**us nerve: T10
Aorta, **A**zygos vein, **T**horacic duct: T12

EXTERNAL ANATOMY

Landmarks outline the location of the lungs and surrounding pleural cavities (see Figure 10-15).

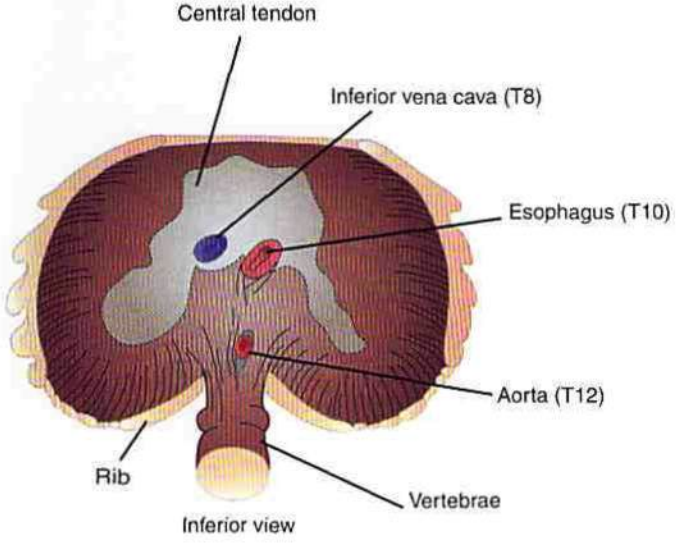


FIGURE 10-14. The diaphragm and penetrating structures.

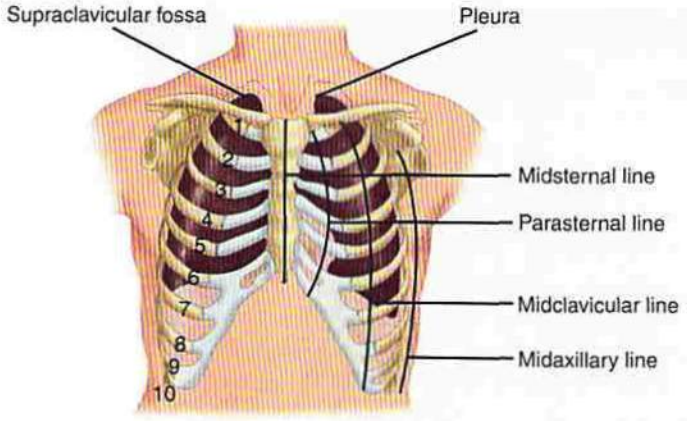


FIGURE 10-15. External landmarks of the thoracic cavity.

- The lungs reach more superiorly than the first rib, into the **supraclavicular fossa**.
- The lower lung borders extend to the sixth rib anteriorly, the eighth rib at the midaxillary line, and the tenth rib posteriorly.
- The pleural reflection extends to the eighth rib anteriorly, descending to the level of the tenth rib at the midaxillary line, and to the 12th rib posteriorly.

MNEMONIC

The intercostal **V**ein, **A**rtery, and **N**erve travel in a **VAN** inferior to the rib.

These landmarks are important when performing thoracic procedures. A **thoracentesis** allows for sampling of pleural effusions by introducing a needle into the pleural space. The needle is typically inserted **above** the rib, because the intercostal vein, artery, and nerve travel along the inferior margin of each rib (see Figure 10-16).

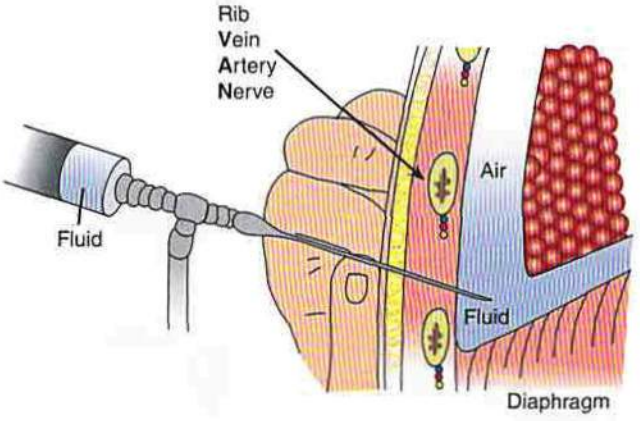


FIGURE 10-16. Thoracentesis.

MECHANICS OF RESPIRATION

The diaphragm is the primary muscle involved in respiration. It is innervated by the **phrenic nerve**, which is formed by branches of the C3, C4, and C5 nerve roots.

The diaphragm is the only muscle involved in **quiet respiration**, or breathing that occurs during rest; multiple accessory muscles are involved in **forced respiration**, which occurs during heavy activity.

HISTOLOGY

Olfactory Cells

In the nasal cavity, the pseudostratified **olfactory epithelium** is found in the superior conchae. Among other supportive cells in this epithelium, **olfactory cells** are bipolar neurons that generate action potentials in response to specific odor molecules. Each olfactory cell has a single dendrite containing a few nonmotile cilia that increase the surface area for olfactory receptors.

Respiratory Epithelium

The respiratory tract is lined mostly by **pseudocolumnar ciliated epithelium** (**"respiratory epithelium"**) from the nasal cavity to the terminal bronchioles, where the lining transitions to simple cuboidal (respiratory bronchioles) and then simple squamous (alveolar ducts and alveoli) epithelium.

Cilia of the respiratory epithelium sweep mucus and foreign particles toward the mouth, providing protection for the lower respiratory tract. **Goblet cells**, which secrete mucus, are interspersed in the pseudocolumnar epithelium from the nasopharynx to the primary bronchioles. These cells can be identified by their distinct shape and pale-staining cytoplasm.

Clara's cells are located in the terminal bronchioles and secrete protein to help protect the airway lining from damage. Microscopically, Clara's cells can be identified by secretory granules located in the apical cytoplasm. They lack cilia.

Alveoli

The alveoli are composed of multiple cell types critical for proper alveolar function. These cells are described in Table 10-3 and illustrated in Figure 10-17.

Pulmonary surfactant, or dipalmitoyl phosphatidylcholine, is produced by type II alveolar cells. It decreases alveolar surface tension and is essential to prevent alveolar collapse. Surfactant is stored in cytoplasmic **lamellar bodies** of type II alveolar cells.

Pulmonary capillary endothelial cells are joined by tight junctions to form a continuous endothelium, without fenestrations. This allows for the sole exchange of gases with the lungs, and prevents any fluid leakage.

CLINICAL CORRELATION

A lesion of the phrenic nerve results in ipsilateral paralysis of the diaphragm. On a chest radiograph, this can be seen as an ipsilateral elevation of the diaphragm.

MNEMONIC

C3, C4, and C5 keep the diaphragm alive.

FLASH BACK

The olfactory cells send axonal processes to the brain via the olfactory nerve (CN I).

FLASH BACK

In **Kartagener's syndrome** (immotile cilia syndrome), a defect in the protein dynein prevents cilia from moving properly. This results in impaired clearance of secretions and frequent respiratory infections, as well as infertility.

FLASH BACK

Alveolar macrophages, which phagocytize RBCs that leak into alveoli in CHF, are also called "heart failure cells."

FLASH BACK

Increased capillary hydrostatic pressure within the lungs, as occurs in severe left ventricular systolic failure, can cause leakage of fluid into the lungs.

TABLE 10-3. Types of Alveolar Cells

	Type I Cells	Type II Cells	Macrophages
Prevalence	97% of alveolar cells.	3% of alveolar cells.	Variable
Structure	Flat.	Large and round.	Amorphous
Function(s)	Allow for gas exchange to the adjacent capillaries.	Secrete surfactant. Proliferate after lung damage. Are source of precursors for new alveolar cells (types I and II).	Engulf debris ("dust cells")

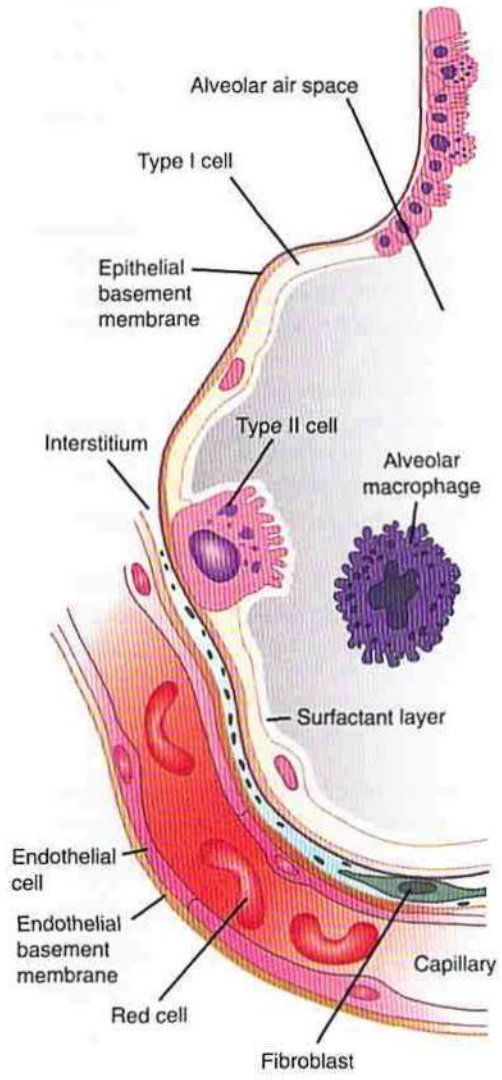


FIGURE 10-17. Alveolar structure.

Physiology

LUNG VOLUMES AND CAPACITIES

- **TV (TV):** The volume of air taken into the lungs during a quiet inspiration (~500 mL) (see Figure 10-18).
- **Inspiratory reserve volume (IRV):** The volume of air that can be inspired beyond the TV during maximal inspiration.
- **Inspiratory capacity (IC)** = TV + IRV.
- **Expiratory reserve volume (ERV):** The volume of air that can be expired beyond normal expiration.
  - **Vital capacity (VC)** = IRV + TV + ERV
    This is equal to the volume of air that can be maximally expired following maximal inspiration. Also known as the forced vital capacity (FVC).
- **Residual volume (RV):** The volume of air that remains in the lungs following maximal expiration.
  - **Functional residual capacity (FRC)** = ERV + RV
    This is equal to the volume of air left in the lungs after a normal, quiet expiration of TV.
- **Total lung capacity (TLC):** The total volume of air in the lungs after maximal inspiration. TLC can be calculated a number of ways:
  TLC = RV + ERV + TV + IRV
  TLC = FRC + IC
  TLC = VC + RV
- **Forced expiratory volume in 1 second (FEV_1):** The volume of air expired in the **first second** of a forced maximal expiration.
- FEV_1 is **normally 80% of the FVC**, or $FEV_1/FVC = 0.8$ (see Figure 10-19 and Table 10-4).

KEY FACT

In obstructive lung diseases, like **asthma or emphysema**, FEV_1 is decreased more than FVC, so **FEV_1/FVC < 0.7–0.8**.
In restrictive lung diseases, like **pulmonary fibrosis**, FEV_1 is decreased to the same extent as, or less than, FVC, so **$FEV_1/FVC \geq 0.7–0.8$**.

Measurement of Lung Volumes

Some lung volumes can be measured simply by having a patient breathe into a spirometer from TLC down to RV. In effect, their respiration equals VC, which is directly calculated. However, since RV (and therefore FRC and

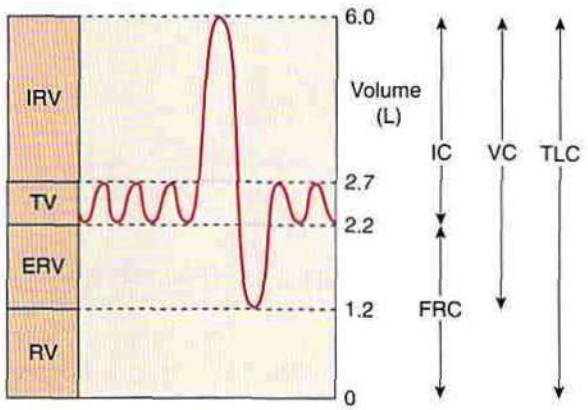


FIGURE 10-18. Lung volumes and capacities. A spirometry tracing showing all of the lung volumes and capacities.

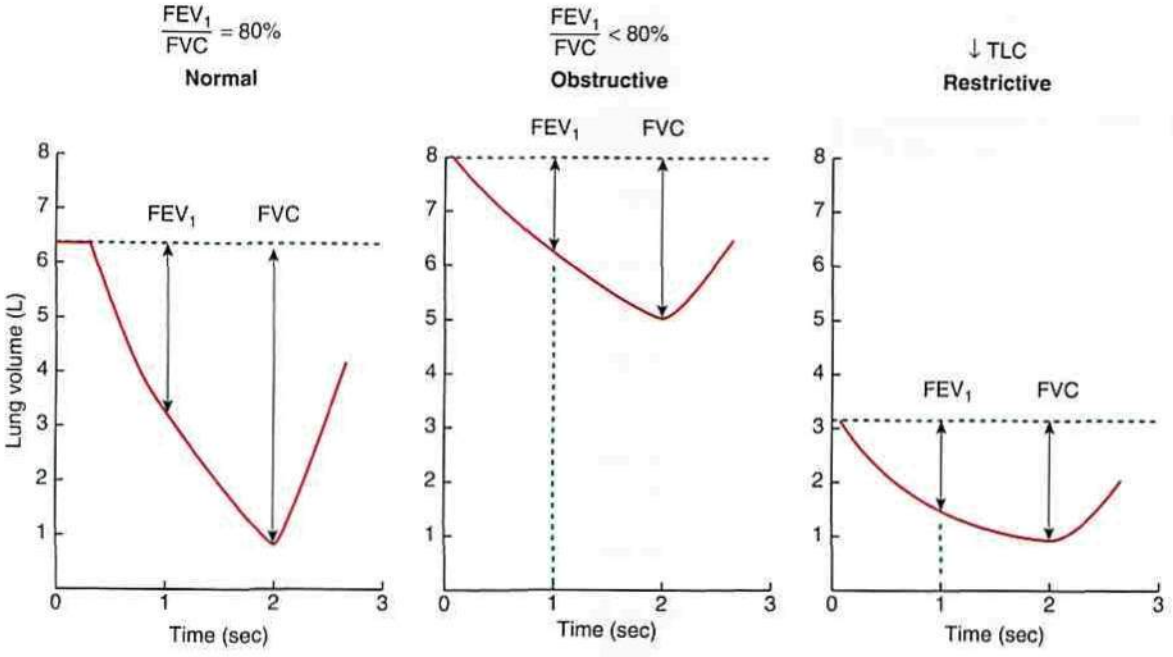


FIGURE 10-19. Obstructive versus restrictive. FVC and FEV_1 in normal subjects and patients with lung disease.

TLC) cannot, by definition, be measured as expired volumes on spirometry, other methods are used. They include:

1. **Dilution tests:** A known volume and concentration of an inert gas (often helium) is inhaled. This inert gas is diluted by the air already in the lungs, so the change in concentration of the gas that is expired can be used to calculate the RV.
2. **Body plethysmography:** The patient sits in an airtight box and performs a maneuver that causes expansion and compression of gas within the thorax. The RV can then be calculated from changes in the gas volume and pressure within the box.

Anatomic Dead Space

The volume of air in the conducting airways that does not participate in gas exchange (everything but the alveoli). It is **normally about 150 mL**, and should be constant.

Physiologic Dead Space (Total Dead Space)

The volume of inspired air that does not participate in gas exchange. Unlike anatomic dead space, this takes into account alveoli that are filled with air but

TABLE 10-4. Lung Volumes in Restrictive versus Obstructive Disease

	RV	FRC	TLC	FVC	FEV1	FEV1/FVC
Obstructive	↑↑	↑	↑	↓	↓↓	↓
Restrictive	↓	↓	↓	↓↓	↓	↑ or normal

are not perfused by blood in the surrounding capillaries (V/Q mismatch). In normal lungs, it is approximately equal to anatomic dead space, but can be greater than anatomic dead space in diseased lungs. Conceptually, dead space (or more specifically V_D/V_T) is proportional to the fraction of TV that reaches areas that do not contribute expired CO_2 (no gas exchange due to absence of perfusion).

$$V_D = V_T \times (PaCO_2 - P_ECO_2)/(PaCO_2)$$

V_D = Physiologic dead space (mL)

V_T = Tidal Volume (mL)

$PaCO_2$ = PCO_2 of arterial blood (mmHg)

P_ECO_2 = PCO_2 of expired air (mmHg)

VENTILATION

Ventilation Rate

Minute Ventilation

The total amount of air inspired in 1 minute.

$$\text{Minute ventilation} = \text{Tidal Volume} \times \text{Breaths/min}$$

Alveolar Ventilation

The total amount of air that reaches the alveoli participating in gas exchange in 1 minute. It is different from minute ventilation due to dead space.

$$\text{Alveolar ventilation} = (\text{TV} - \text{Dead space}) \times \text{Breaths/min}$$

$$V_A \approx VCO_2/PaCO_2$$

V_A = Alveolar ventilation

VCO_2 = CO_2 production in the body

$PaCO_2$ = PCO_2 of arterial blood

Increasing alveolar ventilation through increased depth (TV) or rate of breathing will result in a proportionate decrease $PaCO_2$.

Muscles of Respiration

See Table 10-5.

Inspiration

An **active** process that always requires at least some muscle activity.

- **Diaphragm:** The most important muscle in inspiration. When the diaphragm contracts the volume of the thoracic cavity increases in the vertical dimension. This create negative intrathoracic pressure thus drawing air into the lungs.
- **External intercostals and accessory muscles:** Normally used only during **exercise**, but may be used for inspiration **at rest in patients with lung disease**. These muscles increase the anteroposterior diameter of the chest.

TABLE 10-5. Respiratory Muscles

	Quiet Respiration	Forced Respiration
Inspiration	Diaphragm	Diaphragm External intercostals Scalenes Sternocleidomastoids
Expiration	None (passive)	Rectus abdominis Internal/external obliques Transversus abdominis Internal intercostals

Expiration

Normally passive, secondary to the natural elastic recoil of the lung–chest wall system. The lungs naturally want to return to their RV, so once the active muscle activity of inspiration stops, the lungs recoil back toward RV.

- Expiratory muscles are used during **exercise**, coughing, or when airway resistance is elevated in disease (e.g., **asthma**).
  - Abdominal muscles
  - Internal intercostal muscles

KEY FACT

In **emphysema**, there is destruction of elastic tissue, so **C increases.** In **fibrotic lung disease**, the lungs become stiff, so **C decreases.**

Lung Compliance

Compliance describes the distensibilty of an object. It is **inversely proportional to the amount of elastic tissue, and proportional to the work needed to expand the lungs.** It does not relate to airway resistance.

$$\text{Compliance (C)} = \Delta\text{Volume (V)} / \Delta\text{Pressure (P)}$$

The steeper the curve, the greater the compliance (i.e., a larger volume of air will flow for a given change in pressure). Notice that inspiration follows a different curve than expiration (see Figure 10-20).

Compliance of the Lung–Chest Wall System

Since the act of breathing involves both the lungs and the chest wall, the separate compliance curves for both must be summed in order to understand the mechanics of the respiratory cycle (see Figure 10-21).

Mechanics of Breathing During the Respiratory Cycle

Forces Defined

- **Inward recoil of the lungs:** Inward-directed force created by the elastic tissue in the lungs. In isolation, the lungs will always collapse to a minimal volume, no matter how much air they contain.
- **Outward recoil of the chest wall:** The outward-directed force created by the chest wall's tendency to expand to its resting state (~ 70% of TLC).
- **Intrapleural pressure:** The pressure within the pleural cavity.
- **Intra-alveolar pressure:** The pressure within the alveoli of the lungs. Is the major determinant of air flow into the lungs from the environment.
- **Negative pressure:** Needed for air to flow into the lungs.
- **Positive pressure:** Needed for air to flow out of the lungs.

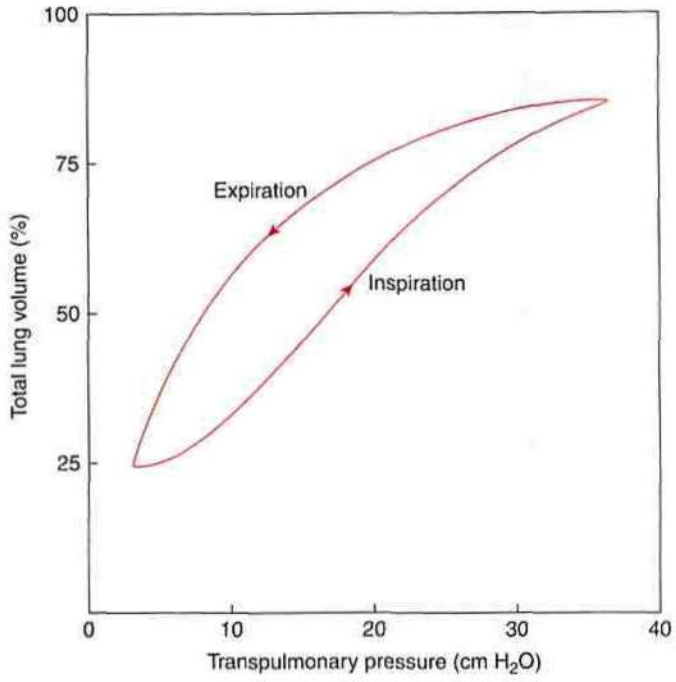


FIGURE 10-20. Hysteresis curve. Compliance (the slope of the curve) changes with inspiration and expiration. Notice that at any given volume, the pressure is lower during expiration than inspiration, and therefore the compliance is greater for a given volume on expiration than on inspiration. (Modified, with permission, from Levitzky MC, *Pulmonary Physiology*, 7th ed, New York: McGraw-Hill, 2007: 20.)

At Rest

At rest, when the gas volume in the lungs is equal to the FRC, the pressures created by the lungs (inward recoil) and the chest wall (outward recoil) are equal and opposite. The lungs create positive pressure, and tend to collapse due to their elasticity. The chest wall creates negative pressure by attempting to expand. These forces cancel out, establishing a distending pressure (alveolar pressure) of 0. The respiratory muscles are not involved in this process.

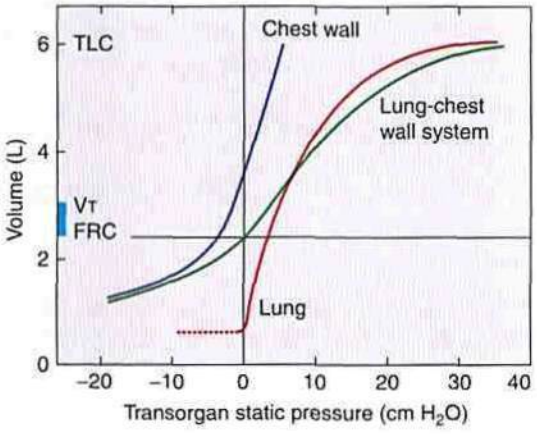


FIGURE 10-21. Lung–chest wall system. Pressure and volume tracings for the lung, chest wall, and the combined system.

Intrapleural pressure = –5 cm H_2O.

Intra-alveolar pressure = 0 cm H_2O.

Since C is increased in **emphysema**, the lungs have a decreased tendency to collapse due to a loss of elasticity. As a result, the lung–chest wall system seeks a new, **higher FRC** at which the forces will balance. This is why patients with emphysema are **barrel-chested**.

Since C is decreased in **lung fibrosis**, the lungs have an increased tendency to collapse. So the system seeks a new, **lower FRC** at which the forces will be balanced.

At Maximum Inspiration

At TLC, the lungs (negative inward elastic recoil) and the chest wall are stretched beyond their resting position, resulting in a positive (inward) pressure (i.e., the chest wall will tend to contract inward). This inward intrapleural pressure is balanced by an equal negative (outward) force created by the muscles of inspiration.

Intrapleural pressure = –8 cm H_2O

Intra-alveolar pressure < 0 cm H_2O, so air flows into the lungs

At Normal Expiration

The muscles of inspiration relax, removing their strong negative (outward) force. This allows the lung–chest wall complex to return to its equilibrium at FRC.

KEY FACT

In a pneumothorax, the negative intrapleural pressure is disturbed by air entering from the environment. The positive pleural pressure leads to collapse of the ipsilateral lung, as well as dissociation of the lung–chest wall system, allowing each to move independently. This contributes to the subjective feeling of dyspnea.

Intrapleural pressure = –5 cm H_2O

Intra-alveolar pressure > 0 cm H_2O, so air flows out of the lungs

At Maximum Expiration

At RV, there is still some gas left in the lungs. That is, **we can never exhale enough to fully collapse the lungs.** At RV, the chest wall is so stiff and exerting such strong negative (outward) pressure, that the expiratory muscles are unable to create enough positive (inward) pressure to exhale any further.

Intrapleural pressure = 20 cm H_2O

Intra-alveolar pressure >> 0 cm H_2O, so air flows out of lungs

Mechanical Ventilation

Mechanical ventilators allow physicians to manipulate the pressures that govern inspiration and expiration. While a detailed explanation of mechanical ventilation is beyond the scope of this text, a brief discussion of the most common modes of mechanical ventilation and how they work may be useful.

- **Assist control:** The ventilator is set to deliver a minimum number of breaths at a set TV, and in effect breathes for the patient. It will automatically deliver the preset volume if the patient initiates a breath. This mode fully supports a patient.

- **Synchronized intermittent mandatory ventilation (SIMV):** The ventilator delivers a specified TV at a predetermined rate. The ventilator breaths are synchronized with patient-initiated breaths. However, if the patient takes an extra breath, the ventilator will not deliver the preset TV, but rather it will let the patient take in their own TV.
- **Pressure support ventilation (PSV):** Each patient-initiated breath is supported by the ventilator providing a specified amount of positive pressure to the airway. The volume of each breath is therefore variable.
- **Positive end-expiratory pressure (PEEP):** PEEP is an option that can be added to other forms of ventilation. With it, airway pressure at the end of expiration falls not to 0, but is instead maintained at a determined value (e.g., 10 cm H_2O). This helps to maintain airway patency during expiration, and is particularly useful in hypoxemic states such as ARDS.

Alveoli

Surface Tension

The collapsing pressure of the alveoli is governed by Laplace's law:

$$P = (2T)/r$$

P = Collapsing pressure

T = Surface tension

r = Alveolar radius

Large alveoli: Have large r, so are easily kept open.
Small alveoli: Have small r, so are prone to collapse (atelectasis).

This explains why alveolar collapse is more likely during expiration (smaller alveoli).

Surfactant

Synthesized by **type II alveolar cells** and is made up primarily of **dipalmitoyl phosphatidylcholine (DPPC).**

- Lines alveoli and acts like a detergent, reducing surface tension. This helps prevent alveolar collapse.
- Surfactant production in the fetus may begin as early as week 24, and is usually present by week 35. A **lecithin:sphingomyelin ratio greater than 2:1** indicates mature surfactant production.
- **Neonatal respiratory distress syndrome** can occur in premature infants due to their lack of surfactant production. These infants have **atelectasis, decreased C,** trouble with inspiration, and **hypoxemia** due to V/Q mismatch.

KEY FACT

Decreased surfactant, a distinguishing feature of ARDS, contributes to decreased compliance and atelectasis.

Other Lung Products

The lung produces some important substances besides surfactant, including:

- Prostaglandins.
- Histamine.
- Kallikrein: Activates bradykinin.
- Angiotensin-converting enzyme (ACE): Converts angiotensin I to angiotensin II; inactivates bradykinin.

KEY FACT

ACE inhibitors increase bradykinin, causing cough and angioedema.

Airways

Flow

Airflow is proportional to the pressure difference between the mouth (or nose) and the alveoli, and is inversely proportional to the resistance of the airway.

$$Q = \Delta P/R$$

Q = Airflow

ΔP = Pressure gradient

R = Resistance

Resistance

Governed by Poiseuille's law:

$$R = (8\eta l)/(\pi r^4)$$

R = Resistance

η = Viscosity of gas

l = Length of airway

r = Radius of airway

Since airway radius is the major determinant of resistance (r^4), the major site of airway resistance is the **medium-sized bronchi** (the smaller bronchi are arranged in parallel, and thus offer less resistance than expected).

Factors that influence pulmonary resistance

- Contraction of bronchial smooth muscle:
  - Sympathetic stimulation: Airways dilate via β_2 receptors, thus decreasing resistance. **Albuterol** is a common β_2 agonist, and is used in an inhaled form by patients with asthma or COPD.
  - Parasympathetic stimulation: Airways constrict, increasing resistance. This is seen in **asthma** as part of the immune response. **Ipratropium** is a common anticholinergic drug used in patients with asthma or COPD that counters this parasympathetic bronchoconstriction.
- Secretions:
  - Increased and/or thickened airway secretions, which are a hallmark of COPD and CF, lead to increased airway obstruction and resistance.
- Lung volumes:
  - High lung volumes: There is greater traction holding the airways open, so resistance is decreased.
  - Low lung volumes: There is less traction and increased resistance. Airways are more prone to collapse.

KEY FACT

Methemoglobinemia may result from treatment with nitrites, and is sometimes induced when amyl nitrite or sodium nitrite is given to treat cyanide poisoning. Methemoglobinemia is treated by administering methylene blue, which provides an artificial electron acceptor to reduce the methemoglobin.

OXYGEN AND CARBON DIOXIDE

Oxygen Transport

Hemoglobin

- **Structure:** Hemoglobin is a globular protein made up of four subunits (2 α chains and 2 β chains). Each contains a **heme moiety**, which is iron-containing porphyrin. The iron in hemoglobin is in the **ferrous** (Fe^{2+})

state, and can bind O_2. If the iron is in the **ferric** (Fe^{3+}) state, it is called **methemoglobin**, and **is unable to bind O_2**.

- **O_2 capacity:** The maximum amount of O_2 that can be bound to hemoglobin. It is dependent upon hemoglobin concentration, and is measured at 100% saturation.
- **O_2 content:** The total amount of O_2 in the blood, both dissolved and bound to hemoglobin. Dependent upon hemoglobin concentration, P_{O_2}, and the P_{50} of the hemoglobin. Calculated by the equation:
  - O_2 content = O_2 bound to hemoglobin + O_2 dissolved in blood
  - O_2 content = (1.34 × Hemoglobin × Saturation) + (0.0031 × Pa_{O_2})
- Thus, the O_2 bound to hemoglobin makes up by far the majority of total O_2 content.

Oxygen-Hemoglobin Dissociation Curve

When the curve shifts to the right (see Figure 10-22), the decreased affinity of hemoglobin for O_2 promotes O_2 unloading to the tissues.

- An increase in P_{CO_2}, altitude, 2,3 diphosphoglycerate (2,3 DPG), temperature, or metabolic needs, or a decreased pH, causes a rightward shift of the curve.
- A decrease in P_{CO_2}, altitude, 2,3 DPG, temperature, or metabolic needs, or an increased pH, causes a leftward shift of the curve.
- In exercise, P_{CO_2} and temperature rise, and pH falls. This promotes a right shift and O_2 unloading to the tissues.
- At high altitudes, 2,3 DPG synthesis is increased, facilitating O_2 unloading.
- Fetal hemoglobin does not bind 2,3 DPG as strongly as adult hemoglobin, shifting the curve to the left and promoting O_2 uploading onto hemoglobin. This helps the fetus obtain O_2 from the mother's RBCs.
- At a **P_{O_2} of 60–100 mmHg**, hemoglobin is 100% saturated. **Arterial blood** has a P_{O_2} of around 100 mmHg.
- At a **P_{O_2} of 40 mmHg**, hemoglobin is 75% saturated. **Venous blood** is at this level of oxygenation.
- At a **P_{O_2} of 25 mmHg**, hemoglobin is 50% saturated. This is the P_{50} (50% saturation point) of hemoglobin.

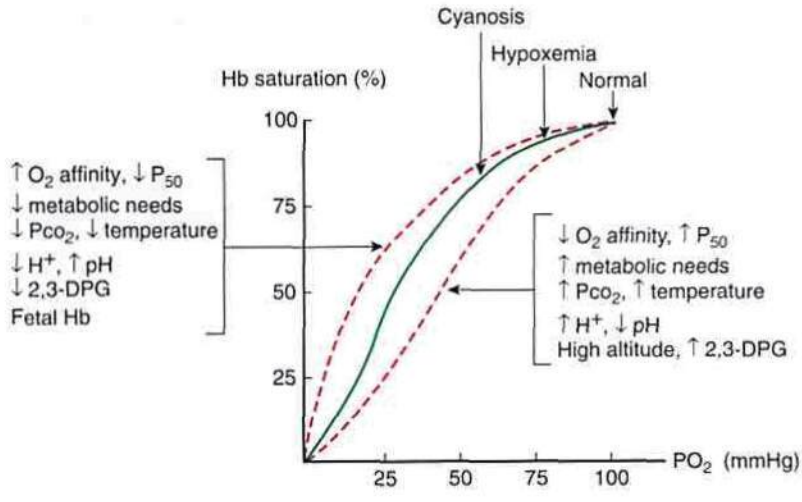


FIGURE 10-22. O_2-hemoglobin dissociation curve. The dashed lines indicate a right or left shift. 2,3 DPG = 2,3 diphosphoglycerate.

MNEMONIC

A good mnemonic for factors that cause a right shift of the O_2-hemoglobin dissociation curve is **CADET**:

C: Increased P_{CO_2}
A: Increased **A**ltitude
D: Increased 2,3 **D**PG
E: **E**xercise
T: Increased **T**emperature

KEY FACT

Carbon monoxide (CO) binds to hemoglobin with 240 times greater affinity than O_2, creating an *allosteric change in the hemoglobin* that prevents the unloading of O_2 from the three other binding sites. This causes a left shift of the curve, and results in hypoxemia in CO poisoning. Treatment includes high-flow O_2 to competitively remove the CO from hemoglobin.

Carbon Dioxide Transport

CO_2 is produced in the body's tissues and carried to the lungs via the venous blood. It is transported in three forms:

1. Dissolved CO_2, which is free in the bloodstream.
2. Carbaminohemoglobin, which is CO_2 bound to hemoglobin.
3. HCO_3^-, formed by the combination of CO_2 and H_2O by the enzyme **carbonic anhydrase**. This is the **major form**.

This reaction reverses in the lungs, where HCO_3^- enters RBCs in exchange for Cl^-, and CO_2 is expired (see Figure 10-23).

In the lungs, the oxygenation of hemoglobin promotes the dissociation of CO_2 from hemoglobin. This is known as the **Haldane effect** (see Figure 10-24).

Respiratory Acid-Base Disturbances

The lungs and kidneys are the major determinants of acid–base balance within the body. The kidneys can eliminate and reabsorb both base (HCO_3^-) and acid (H^+ and fixed acids) in the urine, while the lungs remove volatile acid from the circulation in the form of exhaled CO_2.

- **Respiratory acidosis:** Caused by a **decrease in alveolar ventilation** and retention of CO_2 (**$PaCO_2$ > 40 mmHg**), leading to an increase in blood [H^+] and [HCO_3^-].
  - Renal compensation: Increased excretion of H^+ and NH_4^+ and increased reabsorption of HCO_3^-.
  - Acute respiratory acidosis: Renal compensation has not yet occurred. Each 10-mmHg increase in $PaCO_2$ leads to 1 mEq/L rise in HCO_3^- and 0.08 decrease in pH.
  - Chronic respiratory acidosis: Renal compensation has occurred. Each 10-mmHg increase in $PaCO_2$ leads to 4 mEq/L rise in HCO_3^- and 0.03 decrease in pH.
  - Causes of respiratory acidosis include opiates, sedatives, and anesthetics (due to inhibition of the medullary respiratory center), Guillain–Barré syndrome, ALS, MS (due to weakening of respiratory muscles), airway obstruction, ARDS, and COPD (due to decreased CO_2 exchange).
- **Respiratory alkalosis:** Caused by an **increase in alveolar ventilation** and a loss of CO_2 (**$PaCO_2$ < 40 mmHg**), leading to a decrease in blood [H^+] and [HCO_3^-].
  - Renal compensation: Decreased excretion of H^+ and NH_4^+, decreased reabsorption of HCO_3^-.
  - Acute respiratory alkalosis: Renal compensation has not yet occurred. Each 10-mmHg decrease in $PaCO_2$ leads to 2 mEq/L decrease in HCO_3^- and a 0.08 rise in pH.

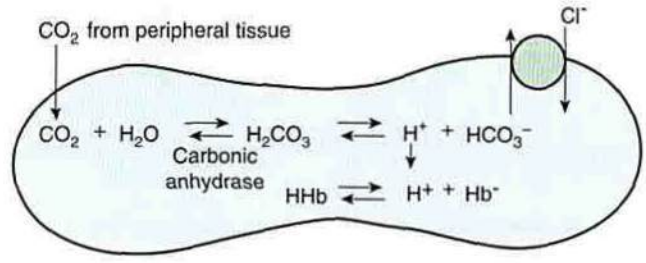


FIGURE 10-23. CO_2 transport. CO_2 handling in the RBC. HHb = de-ionized hemoglobin. (Modified, with permission, from Ganong WF, *Review of Medical Physiology*, 22nd ed, New York: McGraw-Hill, 2005: 670.)

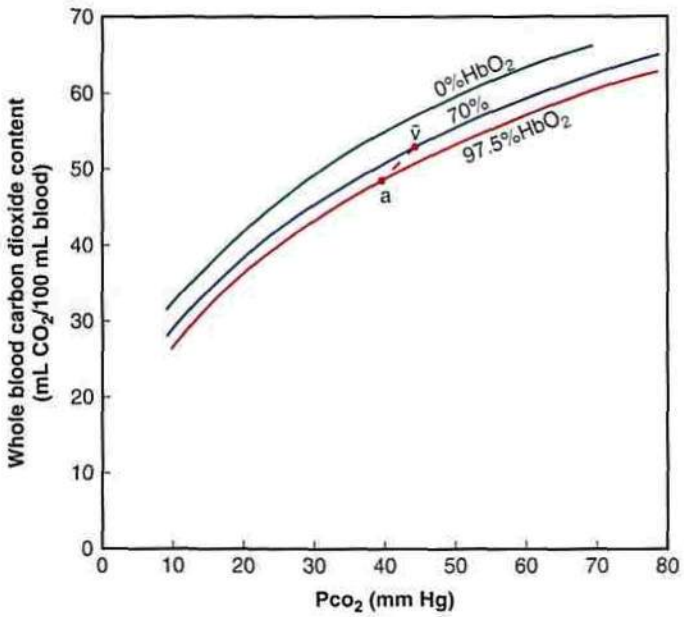


FIGURE 10-24. Haldane effect. As RBCs pass through the alveolar capillaries and the P_{O_2} increases from 70% to almost 100%, the CO_2 dissociation curve shifts downward. This promotes the dissociation of CO_2 from the RBCs. (Modified, with permission, from Levitzky MG, *Pulmonary Physiology*, 7th ed, New York: McGraw-Hill, 2007: 157.)

- Chronic respiratory alkalosis: Renal compensation has occurred. Each 10-mmHg decrease in $PaCO_2$ leads to 5 mEq/L decrease in HCO_3^- and a 0.03 rise in pH.
- Causes of respiratory alkalosis include pulmonary embolism, high altitude (due to hypoxemia and increased ventilation rate), psychogenic, pregnancy, cirrhosis, and salicylate intoxication (due to direct stimulation of the medullary respiratory center).

- **Metabolic acidosis:** Overproduction of fixed acid or loss of base increases arterial $[H^+]$ and decreases $[HCO_3^-]$. The respiratory compensation is to blow off CO_2 and thereby raise the pH by **hyperventilating (Kussmaul's respirations)**.
  - Each 10-mEq/L decrease in HCO_3^- leads to a 10-mmHg decrease in $PaCO_2$.
  - The expected $PaCO_2$ can be estimated by the following formula:
  - Expected $PaCO_2 = 1.5(HCO_3^-) + 8 \pm 2$.
  - Anion gap = $Na - (Cl + HCO_3^-)$.
  - Causes of anion-gap metabolic acidosis include **MUDPILES**: Methanol, Uremia, Diabetic ketoacidosis, Paraldehyde, Iron or isoniazid, Lactic acid, Ethanol or ethylene glycol, and Salicylates. Causes of non anion-gap metabolic acidosis include diarrhea and renal tubular acidosis.
- **Metabolic alkalosis:** Loss of fixed $[H^+]$ or gain of base leads to a decrease in arterial $[H^+]$ and an increase in arterial $[HCO_3^-]$. The respiratory compensation is to retain CO_2 and thereby lower the pH by **hypoventilating**.
  - Each 10-mEq/L increase in HCO_3^- leads to a 7-mmHg increase in $PaCO_2$.
  - The expected $PaCO_2$ can be estimated by the following formula:
  - Expected $PaCO_2 = 0.7(HCO_3^-) + 21 \pm 2$
  - Causes of metabolic alkalosis include vomiting (due to loss of H^+ and volume contraction), hyperaldosteronism (increased H^+ secretion in the distal tubule), and loop or thiazide diuretics (volume contraction alkalosis).

- Whenever the compensation differs from what is expected, suspect a mixed acid-base disorder.

Pulmonary Circulation

Characteristics

The pulmonary vasculature has unique characteristics that set it apart from the rest of the vascular system.

- **Pressures** are much **lower** in the pulmonary circulation than in the systemic circulation (pulmonary arterial pressure = 25 mmHg systolic and 10 mmHg diastolic).
- **Resistance** is much **lower** than in the systemic circulation.
  - Normal pulmonary vascular resistance (PVR) = 20–120 dynes/s/cm^{-5}. This is ~ 1/10 of systemic vascular resistance (SVR) (see Table 10-6).
  - PVR changes with lung volume. At high volumes, the **alveolar vessels** are compressed by stretched alveolar walls, and contribute more to PVR. At low volumes, larger **extra-alveolar pulmonary vessels** are compressed due to decreased elastic traction, and contribute more to resistance.
  - Total PVR is least at FRC.

Distribution of Pulmonary Blood Flow

When a person is supine, blood flow is nearly uniform throughout the entire lung. When standing, however, the lungs are divided into three zones based upon blood flow and ventilation as affected by gravity (see Figure 10-25). Both are increased as one moves down the lung due to gravity, but blood flow increases to a greater degree than ventilation, resulting in a mismatch between ventilation (V) and perfusion (Q). This is V/Q mismatch.

- **Zone 1:** Blood flow is much lower than ventilation here.
  - Alveolar pressure > arterial pressure > venous pressure.
  - High alveolar pressures compress the capillaries and reduce blood flow.
  - Q is reduced compared to V, therefore V/Q is increased. In extreme cases this can approach dead space (Q = 0, so V/Q = 8).
  - P_{O_2} is the highest and P_{CO_2} is the lowest due to increased gas exchange.
- **Zone 2:** Blood flow is at a medium level compared with ventilation here.
  - Arterial pressure > alveolar pressure > venous pressure.
  - Blood flow here is driven by the difference between arterial and alveolar pressures.
- **Zone 3:** Blood flow is greater than ventilation here.
  - Arterial pressure > venous pressure > alveolar pressure.
  - Blood flow here is driven by the difference between arterial and venous pressures, as in the systemic circulation.

TABLE 10-6. Calculating Cardiac Output (CO), PVR, and SVR

	Calculation	Normal Value
CO	SV × HR	5–6 L/min
PVR	(Mean PA pressure – Mean LA pressure)/(CO) × 80	20–120 dynes/s/cm^{-5}
SVR	(Mean arterial pressure – Mean RA pressure)/(CO) × 80	770–1500 dynes/s/cm^{-5}

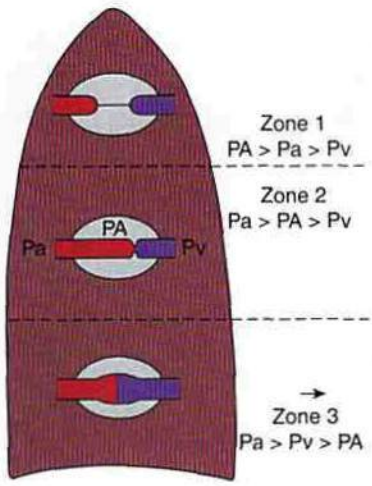


FIGURE 10-25. Three lung zones. Illustration showing the relationships between alveolar pressure (PA), arterial pressure (Pa), and venous pressure (Pv) in the three lung zones.

- Q is greater than V, so V/Q is decreased. In extreme cases, this can approach shunt (V = 0, so V/Q = 0).
- P_{O_2} is the lowest and P_{CO_2} is the highest due to decreased gas exchange.

Regulation of Pulmonary Blood Flow

- **Hypoxia:** In the lungs, hypoxia leads to **vasoconstriction**. This is in contrast to other organs, in which hypoxia leads to vasodilation. Hypoxic vasoconstriction allows blood to be redirected away from poorly ventilated regions and towards well-ventilated areas.
- Several other factors also affect pulmonary blood flow (see Table 10-7).

Hypoxemia

Hypoxemia is defined as a below-normal O_2 content in the arterial blood, usually indicated by a reduced Pa_{O_2}. In a normal individual, the blood leaving the lungs should have an O_2 tension (Pa_{O_2}) approximately equal to the O_2 tension within the alveoli (PA_{O_2}).

$$PA_{O_2} = FI_{O_2}(P_B - P_{H_2O}) - (PA_{CO_2}/R)$$

FI_{O_2} = Fractional content of inspired O_2 (0.21 on room air)

P_B = Barometric pressure (760 torr at sea level)

P_{H_2O} = Vapor pressure of H_2O in the alveoli (47 torr at 37°C)

PA_{CO_2} = Alveolar CO_2 tension

R = Respiratory quotient (0.8)

For a patient breathing room air, this can be simplified to:

$$PA_{O_2} = 150 - 1.25(Pa_{CO_2})$$

Once PA_{O_2} is calculated, the expected Pa_{O_2} can be measured via arterial blood gas testing. The difference between the PA_{O_2} and Pa_{O_2} is the alveolar-

KEY FACT

Pulmonary blood flow can be measured using radioactive isotopes. This method, called **V/Q scanning,** can detect areas of decreased perfusion, and is useful for evaluating for pulmonary embolisms and assessing regional lung function.

KEY FACT

In the fetus, PVR is very high due to hypoxic vasoconstriction. This allows blood to be diverted away from the developing lungs. When the infant is born and begins to breathe, the PVR decreases.

TABLE 10-7. Other Regulatory Factors and PVR

	Low pH	Histamine	Prostaglandins	Nitric Oxide	Endothelin	Sympathetic Tone	Parasympathetic Tone
Vasoconstriction	X				X	X	
Vasodilation		X	X	X			X

arterial O_2 gradient ($AaDO_2$), and should be **less than 15 torr**, although this value can increase with normal aging.

Etiology

There are five main causes of hypoxemia. They include:

1. **Hypoventilation:** Hypoventilation is relatively common in lung disease. It is characterized by a reduced PaO_2 and an **increased Pa_{CO2}**. Since alveolar ventilation is also reduced, there is **no increase in $AaDO_2$**.
2. **Decreased inspired O_2:** This occurs most commonly at high altitudes, where the barometric pressure (PB) is decreased. This causes a reduction in PaO_2 due to the decrease in PAO_2. Thus, there is **no increase in $AaDO_2$**.
   - There are several physiologic adaptations to high altitude (see Table 10-8).
3. **Poor gas exchange (diffusion impairment):** This is a rare cause of hypoxemia, due to a failure of PO_2 in the pulmonary capillary blood to equilibrate with alveolar gas. The **$AaDO_2$ is increased.**
   - O_2 is normally a **perfusion-limited** gas. This means that O_2 equilibrates early along the length of the pulmonary capillary (within the first one-third). This leaves a lot of room for compensation in disease states, and thus, a failure in O_2 diffusion is a very rare cause of hypoxemia.
   - O_2 can become a **diffusion-limited** gas under certain circumstances, in which case it does not equilibrate by the end of the pulmonary capillary, resulting in the maintenance of a partial pressure gradient

TABLE 10-8. Response to High Altitude

Parameter	Response
PaO_2	Decreased
PAO_2	Decreased
Ventilation rate	Increased
Arterial pH	Increased
Hemoglobin concentration	Increased
2,3-DPG concentration	Increased
Hemoglobin-O_2 curve	Right shift
PVR	Increased

between the alveolus and the capillary. This can occur in **strenuous exercise** (due to increased flow rates), **pulmonary fibrosis** (due to alveolar membrane thickening), and **emphysema** (due to decreased surface area for gas diffusion).
- Even when there is an abnormality in diffusion, it is usually not great enough to cause hypoxemia unless the patient is exercising.
- Diffusion capacity can be measured using cardiac output, resulting in a D_{LCO} value. This value is a surrogate for the surface area available for gas exchange.
  - D_{LCO} is decreased in emphysema, interstitial lung disease, and pulmonary vascular disease.
  - D_{LCO} may be increased when there is intraparenchymal hemorrhage.

4. **Shunt:** Shunt occurs when some blood reaches the systemic circulation without being oxygenated in the lungs (V/Q = 0). This deoxygenated blood combines with oxygenated blood from the lungs, reducing P_{aO_2}. Since the P_{AO_2} is unaffected, the **A_aDO_2 is increased.**
   - **Right-to-left shunt:** Occurs when blood from the right side of the heart enters the systemic circulation without passing through the lungs. It is seen in **tetralogy of Fallot** (and other congenital heart disease causing right-to-left shunts), and always causes a reduction in P_{aO_2}.
   - **Left-to-right shunt:** Is more common than right-to-left shunt, because pressures are higher on the left side of the heart. It is seen with several congenital abnormalities, including a patent ductus arteriosus, or traumatic injury. Left-to-right shunts **do not decrease P_{aO_2}**, since oxygenated blood is returning to the right side of the heart, raising the P_{O_2}.
   - True shunt can be differentiated from V/Q mismatch by giving the hypoxemic patient 100% O_2. In shunt, increasing inspired F_{IO_2} does not substantially increase P_{aO_2}. In V/Q mismatch, 100% O_2 will increase P_{aO_2}.
5. **V/Q mismatch:** The V/Q ratio is the ratio of ventilation to pulmonary blood flow, or perfusion. Under normal circumstances, V/Q ≈ 0.8, although it varies with the position in the lungs being highest at the apices and lowest at the bases. When the V/Q ratio is altered from this normal value, hypoxemia can result. There is also an **increased A_aDO_2 gradient.**
   - **V/Q mismatch in airway obstruction:** If the airway is completely blocked and blood flow remains, then V = 0, so V/Q = 0, and there is a **shunt**. Since there is no gas exchange, the values of P_{O_2} and P_{CO_2} for pulmonary capillary blood will approach the values of mixed venous blood (P_{aO_2} = 40 mmHg, P_{aCO_2} = 46 mmHg).
   - **V/Q mismatch in pulmonary embolism:** If blood flow is completely blocked, then Q = 0, so V/Q = ∞, and there is **dead space.** This results in increased CO_2 retention, although this is rarely seen since patients with pulmonary embolism (PE) will often hyperventilate, and may even become hypocapnic as a result. Local bronchospasm due to the PE can also contribute to hypoxemia.
   - In most cases of V/Q mismatch, there is neither true shunt nor dead space, but simply a **reduced V/Q ratio.** Areas with a decreased V/Q ratio contribute relatively desaturated blood (low O_2 content) to the systemic circulation. Blood from well-ventilated areas cannot compensate for this, since the hemoglobin of this blood is already fully saturated and cannot increase its O_2 carrying capacity, even with increased ventilation. In this case, giving the patient **100% O_2 will increase the patients P_{aO_2}.**

CLINICAL CORRELATION

Over time, left-to-right shunt can cause pressures on the **right side** of the heart to be greater than those on the **left**. This leads to a reversal of the shunt to right-to-left, causing hypoxemia. This is called **Eisenmenger's syndrome**.

Hypercapnia

Alveolar ventilation is the main determinant of $PaCO_2$. Hypercapnia will occur when alveolar ventilation is reduced, which can happen in a number of ways:

- Decreased total minute ventilation without a change in the V_D/V_T ratio.
- Constant minute ventilation with increasing V_D/V_T. This can occur with decreased TV (a greater percentage of the TV is taken up by dead space) and increased respiratory rate.
- V/Q mismatch. Well-perfused areas may be underventilated, while underperfused areas may be over ventilated. When a large amount of ventilation goes to underperfused sections of lung, the effect is similar to increasing the dead space. The portion of the lung with good perfusion is underventilated, reducing effective alveolar ventilation. These combine to result in hypercapnia.

The response of the body to hypercapnia is often to increase alveolar ventilation by hyperventilating and blowing off more CO_2. Thus, CO_2 retention may not occur even if the above criteria are met.

Control of Respiration

Central Control of Respiration

- **Medullary respiratory center:** Located in the reticular formation. Damage to this region due to stroke or other incident can lead to respiratory failure and death.
  - Dorsal respiratory group: Responsible for inspiration, and determines the rhythm of breathing. The vagus and glossopharyngeal nerves transmit information from the peripheral chemoreceptors and mechanoreceptors in the lungs. Output travels via the phrenic nerve to the diaphragm.
  - Ventral respiratory group: Responsible for expiration, and is not active during passive expiration in normal breathing.
- **Pneumotaxic center:** Located in the upper pons. Inhibits inspiration, helping to regulate inspiratory volume and rate.
- **Apneustic center:** Located in the lower pons. Stimulates inspiration.
- **Cerebral cortex:** Exerts voluntary control over breathing.

Chemoreceptors

- **Central chemoreceptors in the medulla:** Respond to the pH of the CSF, with decreases in pH causing hyperventilation. CO_2 from arterial blood diffuses into the CSF and combines with H_2O to form H^+ and HCO_3^-.
- **Peripheral chemoreceptors in the carotid and aortic bodies:** Increased $PaCO_2$ or decreased pH or PaO_2 stimulate these chemoreceptors to increase respiratory rate. PaO_2 must reach quite low levels (< 60 mmHg) before breathing is stimulated.

Other Receptors

- **Lung stretch receptors:** Located in the airway smooth muscle, these receptors are stimulated by distention of the lungs and produce a reflex decrease in breathing rate (Hering–Breuer reflex).
- **Irritant receptors:** Located between airway epithelial cells and stimulated by noxious substances.
- **J receptors:** Located close to the capillaries in the alveolar walls. Dilation of the pulmonary capillaries, as occurs in heart failure, stimulates these receptors, causing rapid, shallow breathing.
- **Joint and muscle receptors:** These are activated by limb movement, and help to stimulate breathing early in exercise.

Pathology

OBSTRUCTIVE LUNG DISEASES

Obstructive lung diseases are a group of disorders whose distinguishing feature is **airflow obstruction**. The three major obstructive disorders comprise **chronic obstructive pulmonary disease (COPD)**, including emphysema and chronic bronchitis, asthma, and bronchiectasis. Airflow obstruction can originate at any point in the respiratory tree, from the bronchioles to the main stem bronchi. All lead to a marked decrease in forced expiratory volume in 1 second (FEV_1), a normal or increased forced vital capacity (FVC), and therefore a **decreased FEV_1:FVC ratio**. This is the hallmark of obstructive lung disease.

Emphysema

Destruction of alveolar walls leads to the **loss of elastic recoil** within the lung and **dilation of the terminal air spaces.**

- Proteolytic enzymes (i.e., elastase) digest elastin, the component responsible for elastic recoil in alveolar walls. Enzymes like α_1-antitrypsin prevent elastase from being active constituently.
  - **Smoking:** Cigarette smoke acts by attracting neutrophils and macrophages, which produce elastase, and by inactivating α_1-antitrypsin.
  - **Hereditary α_1-antitrypsin deficiency:** This makes up a small subgroup of cases of emphysema (approximately 1%).
- The loss of elastic recoil in the lung parenchyma shifts the compliance curve of the lung upward and to the left (see Figure 10-26), resulting in:
  - Decreased driving pressure for expiratory airflow, which leads to prolonged expiration to maximally empty the lungs.
  - Loss of radial traction on the airways due to destruction of parenchymal tissue. This leads to airway collapse during expiration and air trapping.

The prolonged expiratory phase seen in emphysema lengthens the overall length of a single respiratory cycle. Since patients need to ventilate at a high enough rate to remain oxygenated despite the prolonged respiratory cycle, patients will often begin inhaling their next breath before all of the air from the previous breath is expired. This traps the nonventilated air in their lungs. Over time, they breathe at higher and higher volumes (dynamic hyperinflation).

PRESENTATION

Chronic dyspnea with or without cough. Dyspnea and desaturation are often worsened by exertion, and can be exacerbated by respiratory tract infections, air pollutants, bronchospasm, or CHF.

- **"Pink puffer"**: Arterial P_{O_2} is well preserved, so patients are not cyanotic ("pink"). While ventilation and perfusion are both decreased, they are often well matched, so V/Q mismatch is not severe. Patients require a high minute ventilation to maintain normal levels of P_{O_2} and P_{CO_2}, and so "puff," working hard to get air in. Although this is the classic presentation, many patients do not fit this description.

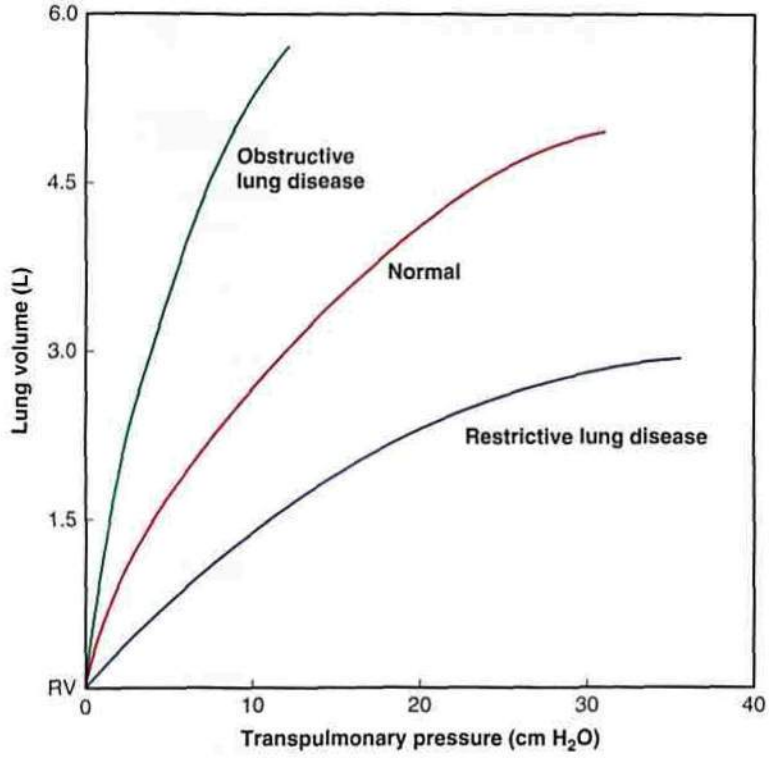


FIGURE 10-26. Lung compliance in pulmonary disease. The lung compliance curve shifts up and to the left in COPD, and down and to the right in restrictive lung disease.

Diagnosis

- Physical exam:
  - Thin or cachectic
  - Leaning forward on extended arms ("tripoding"), using accessory muscles of respiration
  - Increased anteroposterior (AP) diameter of the chest, due to hyperinflation of the lungs
  - Prolonged expiration, with decreased breath sounds. Occasionally, wheezes on forced exhalation
- **Chest X-ray:** Hyperinflated lungs, flattened diaphragm, and increased AP diameter. Paucity of vascular markings (arterial deficiency) in the upper lobes with or without bullae in classic emphysema. These changes can be seen in the lower lobes in α_1-antitrypsin deficiency.
- **Pulmonary function testing:** Decreased FEV_1 and FEV_1:FVC ratio. FVC is often preserved. Air trapping leads to increased TLC, FRC, and RV.
- **Diffusing capacity:** Surface area for gas exchange decreased, so DLCO decreased.
- **Arterial blood gas testing:** Both PaO_2 and $PaCO_2$ are normal or slightly decreased. During acute exacerbation, PaO_2 may drop and $PaCO_2$ may rise, with a corresponding drop in pH.
- **Pathology:** Two major subtypes of emphysema.
  - **Panacinar (panlobar) emphysema:** Characterized by dilation of the entire acinus (including the respiratory bronchioles, alveolar ducts, and alveolar sacs), distributed uniformly throughout the lung. Associated with α_1-antitrypsin deficiency.
  - **Centriacinar (centrilobular):** Characterized by dilation of the proximal part of the acinus (the respiratory bronchioles). The pattern of involvement is more irregular, and is often localized to the upper parts of the lungs. Associated with smoking.

Treatment

Inhaled bronchodilators (β_2-agonists [albuterol, salmeterol] or anticholinergics [ipratropium, tiotropium]) can reduce airflow obstruction. IV or PO corticosteroids are used during acute exacerbations, and are given long-term via inhaler for chronic disease. Supplemental O_2 is useful in patients with hypoxemia. Lung volume reduction surgery has been found to benefit a small subset of COPD patients, but may not be appropriate for the majority of COPD patients. Pulmonary rehabilitation is often helpful.

Prognosis

Lifelong and chronic. Often coexists with, or may be complicated by, chronic bronchitis. Pneumothorax can occur due to rupture of a surface bleb or tear in the airways.

Spontaneous Pneumothorax

The classic patient is a tall, thin young male describing sudden onset of shortness of breath and chest pain, often without exertion. The rupture of a lung bleb (a fluid-filled sac) is usually the cause of lung collapse. The deflated lung produces the following signs upon examination of the ipsilateral chest:

- Asymmetrical expansion
- Absent fremitus
- Hyperresonance on percussion
- Decreased breath sounds
- Tracheal deviation away from the lesion

In addition, the collapsed lung may be identified on a chest radiograph, as shown in Figure 10-27.

Chronic Bronchitis

Defined clinically as a **productive cough** occurring for at least 3 months per year over at least 2 consecutive years. Characterized by excessive mucus

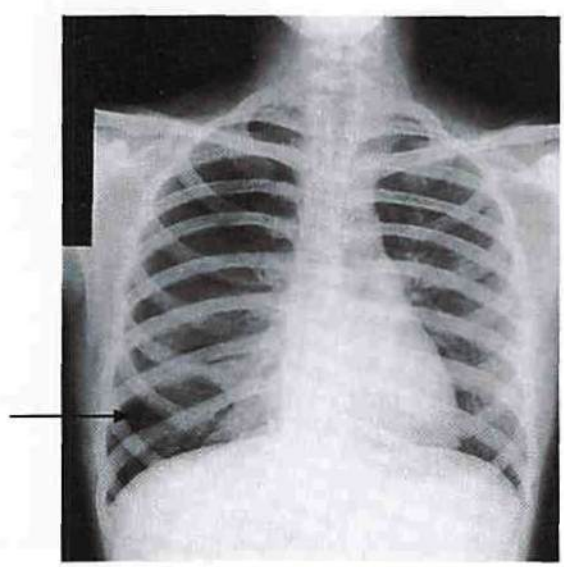


FIGURE 10-27. Spontaneous pneumothorax on the right side. The outline of the right lung is visible (red arrow), abnormally separated from the parietal pleura. (Adapted, with permission, from Doherty GM, Way LW, *Current Surgical Diagnosis & Treatment*, 12th ed, New York: McGraw-Hill, 2006: 349.)

production in the airways. The mucus itself is often more viscous in chronic bronchitis.

- Smoking causes proliferation and hypertrophy of bronchial mucous glands. It also damages cilia lining the bronchial lumen, impeding mucus clearance. There is also an influx of inflammatory cells, leading to airway inflammation.
- The increased mucus production and airway wall thickness decreases the cross-sectional area, increasing resistance and inhibiting air flow.

Presentation

Chronic productive cough, dyspnea.

- **"Blue bloater":** Patients are often hypoxemic and cyanotic ("blue"), due to decreased ventilation in diseased airways with relative preservation of perfusion, resulting in V/Q mismatch. They are also frequently obese and can have peripheral edema due to right ventricular failure ("bloater"). However, there is a great deal of overlap between chronic bronchitis and emphysema in many patients.

Diagnosis

- Physical exam:
  - Often obese and sometimes cyanotic.
  - Breath sounds characterized by wheezing and rhonchi.
- Chest X-ray: Often normal, but there may be evidence of pulmonary hypertension and cor pulmonale.
- Pulmonary function testing: Airflow obstruction results in decreased FEV_1 and FEV_1:FVC ratio. FVC is often preserved. With pure airway disease, TLC and FRC should remain normal. However, in patients with dynamic hyperinflation, FRC and RV may be increased.
- Diffusing capacity: Often normal.
- Arterial blood gas testing: Pa_{O_2} is often decreased and Pa_{CO_2} is increased. Bicarbonate is elevated in an attempt to compensate for the decreased pH.
- Pathology: Increased number of goblet cells. The **Reid index**, which compares the thickness of mucous glands to the thickness of the airway wall, is increased.

Treatment

Bronchodilators and corticosteroids are used as in emphysema. Supplemental O_2 can prevent hypoxemia, reduce hypoxic vasoconstriction and polycythemia, therefore reducing the incidence of pulmonary hypertension. It is the only intervention that has been shown to reduce mortality. Chest physiotherapy (percussion, coughing, and postural changes) can loosen and clear airway secretions, and pulmonary rehabilitation is helpful.

Prognosis

Pulmonary hypertension, secondary to hypoxemia and pulmonary vasoconstriction, and eventually **cor pulmonale** can develop.

Asthma

Affects 3%–5% of the population and is characterized by hyperresponsiveness of the airways, resulting in bronchoconstriction. There are extrinsic and intrinsic subtypes, each with differing underlying pathophysiology.

- Extrinsic asthma: Mediated by a **type I hypersensitivity** reaction involving IgE and mast cells. Often begins in childhood, in patients with a family history of allergy (see Table 10-9).

TABLE 10-9. Common Epithelial-Derived Inflammatory Mediators in Asthma

Inhaled/Luminal Stimuli (e.g., Allergens, Pollutants, Cytokines)	Physiologic Effect(s)
Endothelin-1	Bronchoconstriction
NO PGE_2 15-HETE	Vasodilation
Cytokines: ▪ GM-CSF ▪ IL-8 ▪ RANTES ▪ Eotaxin	Inflammation
Growth factors: ▪ EGF ▪ IGF-1 ▪ PDGF	Fibrosis Small muscle hyperplasia

Contraction of airway smooth muscle, mucosal edema, and secretions within the lumen contribute to airway narrowing, increasing resistance and reducing airflow, especially during expiration. (EGF = Endothelial growth factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IGF-1 = insulin-like growth factor-1; IL-8 = interleukin-8; 15-HETE = 15-hydroxyeicosatetraenoic acid; NO = nitric oxide; PDGF = platelet-derived growth factor; = prostaglandin PGE2 E2.)

- Intrinsic asthma: Includes asthma associated with chronic bronchitis as well as exercise- or cold-induced asthma.

In both, airway inflammation leads to bronchial hyperresponsiveness. Implicated in this inflammation are eosinophils, lymphocytes, histamine, leukotrienes, and IgE. Between attacks, most asthmatics have relatively normal physiology.

KEY FACT

Some asthmatics may be sensitive to aspirin, which inhibits cyclooxygenase and favors the production of leukotrienes (which play a role in airway inflammation and are potent bronchoconstrictors) from arachidonic acid.

Presentation

Cough, dyspnea, wheezing, and chest tightness.

Diagnosis

- Physical exam: Tachypnea. Prolonged expiration and wheezing on auscultation.
- **Methacholine** (a cholinergic agent) or histamine inhalation: Used as a diagnostic tool for bronchoprovocation challenge. When a person with asthma inhales a small dose of one of these agents, they experience bronchoconstriction.
- Pulmonary function testing: During an acute attack, airflow obstruction results in decreased FEV_1 and FEV_1:FVC ratio (FVC is often normal), and dynamic hyperinflation leads to a normal or increased TLC, and an increased FRC and RV (see Figure 10-28). Between attacks, PFTs are often normal, although there may be small changes, such as decreased maximal midexpiratory flow and increased RV.
- Patients with asthma can often monitor their own respiratory status with portable peak flow meters.

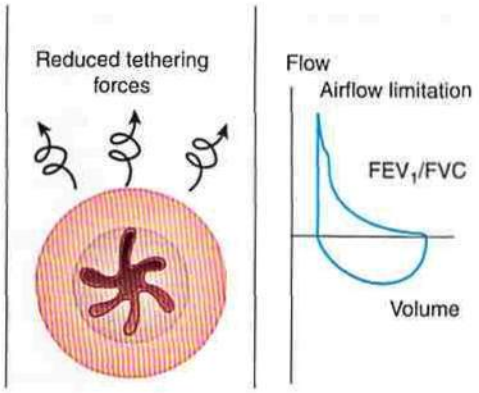


FIGURE 10-28. Changes seen in asthma. The inflammation in asthma leads to airway wall thickening, edema, and mucus secretion. This leads to a restrictive pattern on spirometry. (Modified, with permission, from Hanley ME, Welsh CH, *Current Diagnosis & Treatment in Pulmonary Medicine*, New York: McGraw-Hill, 2003.)

- Arterial blood gas testing: During an attack, PaO_2 is often reduced due to hypoxemia resulting from V/Q mismatch. $PaCO_2$ is also reduced, because patients will hyperventilate. $PaCO_2$ levels that normalize or become elevated during an asthma attack may indicate worsening airway obstruction or a tiring individual who can no longer maintain a high minute ventilation rate.
- Pathology: Edema and cellular infiltrates (eosinophils and lymphocytes) seen in the bronchial wall. Denuding of the epithelium, hypertrophy and hyperplasia of the smooth muscle layer, and enlargement of mucous glands with an increased number of goblet cells are also seen.

Treatment

- **β_2-Agonist** (albuterol) inhalers help bronchodilate and reduce airflow obstruction.
- **Corticosteroids:** Used to reduce inflammation. Inhaled form given to reduce systemic side effects. Oral or parenteral steroids are used in acute, severe attacks.
- **Xanthines** (theophylline): These drugs increase cAMP, leading to airway dilation. They may also have an anti-inflammatory effect.
- **Cromolyn:** Inhibits the release of inflammatory mediators from mast cells.
- **Leukotriene blockers:** Zileuton inhibits 5-lipoxygenase, which reduces the production of leukotrienes. Montelukast and zafirlukast are leukotriene D_4-receptor antagonists.
- **Omalizumab:** Monoclonal antibody that binds circulating IgE, reducing airway inflammation.

Prognosis

May improve with age or be a life-long condition. A severe attack that is refractory to bronchodilators (**status asthmaticus**) may require assisted ventilation and can result in death.

Bronchiectasis

An irreversible dilation of airways caused by inflammatory destruction of airway walls, leading to colonization by bacteria and pooling of secretions. The ability to fight off infection is compromised with constitutive colonization. The bacteria and host may form a stable relationship that can be interrupted

by acute exacerbations of the infection. Bronchiectasis has multiple etiologies, including:

- Infection: May be viral, bacterial, or fungal. Examples include tuberculosis, pertussis, and allergic bronchopulmonary aspergillosis.
- Obstruction, often by tumor.
- A defect in airway clearance of, or protection against, bacterial pathogens can also lead to bronchiectasis. An example is **Kartagener's syndrome** which results in ciliary dysfunction and manifests as **sinusitis, bronchiectasis,** and **situs inversus**.
- Patients with cystic fibrosis also develop bronchiectasis due to the production of thick secretions that are difficult to clear, and chronic infection with multiple pathogens.

PRESENTATION

Cough and copious, purulent sputum production, hemoptysis.

DIAGNOSIS

- Physical exam:
  - Localized crackles or rhonchi may be heard. It is also common to hear squeaks and pops.
  - Clubbing may also be seen in some patients.
- Chest X-ray: Often nonspecific abnormal findings, including increased markings, crowded vessels, or "ring" shadows corresponding to the dilated airways.
- CT: Has become the preferred method both to diagnose bronchiectasis and to evaluate location and extent of disease.
- Pulmonary function testing: Often normal, but can also show obstructive pattern.
- Arterial blood gas testing: Usually normal, except in patients with very diffuse disease, who can exhibit hypoxemia and hypercapnia.
- Pathology: Marked dilation of the airways in one of three patterns: cylindrical, varicose, or saccular. Increased secretions are also seen. The arteries also enlarge and proliferate. New anastomoses may form, leading to hemoptysis (see Figure 10-29).



FIGURE 10-29. Bronchiectasis. Multiple bronchiectatic cavities can be seen on a cut section of lung. (Image courtesy of PEIR Digital Library [http://peir.net].)

FLASH FORWARD

Antipseudomonal drugs include ticarcillin and piperacillin, ciprofloxacin, some third- and fourth-generation cephalosporins, and certain aminoglycosides.

Treatment

Inhaled bronchodilators are useful in patients with coexisting airway obstruction. Antibiotics are given to treat both acute and chronic infections. Bronchopulmonary drainage with physical therapy helps to clear secretions from the dilated airways. In CF patients, DNAse is used to break up thick secretions.

Prognosis

In severe cases, cor pulmonale can develop. Colonization with *Pseudomonas aeruginosa* is frequent.

RESTRICTIVE LUNG DISEASES

Restrictive lung diseases are characterized by reduced expansion of the lungs and a **decrease in TLC. FEV_1 and FVC are both reduced**, but the **FEV_1:FVC ratio is normal or increased**. Main categories of restrictive lung diseases are extrapulmonary disorders, in which the defect is extrinsic to the lung parenchyma, and interstitial lung disease, in which the problem is within the lung parenchyma.

Extrapulmonary Restrictive Disease

Includes disorders of the chest wall or neuromuscular disease.

- **Neuromuscular disease:** Lead to weakness of the respiratory muscles. Patients alter their pattern of breathing, taking more frequent, shallow breaths. This increases the V_D:V_T ratio, reducing alveolar ventilation and increasing $PaCO_2$. Ineffective cough can lead to recurrent respiratory infections, the accumulation of secretions, and atelectasis.
  - Guillain–Barré syndrome
  - Myasthenia gravis
  - Poliomyelitis
  - Post-polio syndrome
  - Amyotrophic lateral sclerosis
- **Diaphragmatic disease:** May lead to hypoventilation and respiratory failure.
  - Diaphragmatic fatigue: Due to increased work of breathing, decreased energy supply to the diaphragm, and inefficient diaphragmatic contraction.
  - Unilateral diaphragmatic paralysis: Due to trauma or disease affecting the ipsilateral phrenic nerve, including impingement by tumor.
  - Bilateral diaphragmatic paralysis: Often due to a neuromuscular cause or phrenic nerve palsy.
- **Diseases affecting the chest wall:** Distortion of the chest wall or diaphragm leads to hypoventilation of lung regions, V/Q mismatch, and occasionally hypoxemia.
  - Kyphoscoliosis: Abnormal curvature of the spine in the lateral and anteroposterior directions. As a result, the rib cage becomes stiffer and more difficult to expand.
  - Obesity: Excess soft tissue makes the chest wall stiffer and less compliant, in addition to exerting pressure on the abdominal contents, forcing the diaphragm up to a higher resting position. One serious consequence of this includes obesity-hypoventilation syndrome, also known as **pickwickian syndrome**, which is characterized by a reduced central drive to breathe.

Presentation

Most often dyspnea, especially with exertion.

Diagnosis

- Physical exam:
  - Neuromuscular disease: Nonpulmonary manifestations of individual neuromuscular disease.
  - Diaphragmatic disease: Paradoxical movement of the diaphragm inward during respiration.
- Chest X-ray: Assess for kyphoscoliosis, diaphragmatic paralysis.
- Respiratory muscle forces (maximal inspiratory [MIP] or expiratory [MEP] pressure): These represent the maximum forces that a patient can generate against a closed mouthpiece, which are then measured. Assesses the strength of the respiratory muscles.
- Pulmonary function testing: Decreased TLC, FRC, RV (except some neuromuscular diseases in which FRC is normal and RV is elevated), FEV_1 and FVC, with a normal or increased FEV_1:FVC ratio.

Treatment

Supplemental O_2 or mechanical ventilation may be needed for patients with severe disease. The underlying disorder must be treated before irreversible pulmonary sequelae develop.

Prognosis

Diseases of the chest wall resulting in hypoxemia can lead to pulmonary hypertension and cor pulmonale. Progressive disease can lead to chronic respiratory acidosis.

INTERSTITIAL LUNG DISEASES

Acute Respiratory Distress Syndrome (ARDS)

A syndrome that results from diffuse alveolar damage and leakage of fluid out of the pulmonary capillaries into the interstitium and alveolar spaces. Causes include pneumonia, inhalation of irritants, O_2 toxicity, heroin overdose, shock, sepsis, aspiration of gastric contents, trauma, uremia, acute pancreatitis, head trauma, multiple transfusions, DIC, and fat or amniotic fluid embolism.

The initial injury in ARDS affects the type I alveolar epithelial and/or capillary endothelial cells, resulting in leakage of protein-rich fluid. Alveoli become flooded with fluid, preventing ventilation. This leads to shunting and V/Q mismatch, causing hypoxemia. Surfactant function and production is altered, resulting in alveolar collapse. Pulmonary vascular resistance increases, changing the distribution of pulmonary blood flow and leading to further V/Q mismatch. The net result of alveolar filling is a reduction in pulmonary compliance. ARDS is defined by the following criteria:

- Bilateral infiltrates
- $P_{O_2}/F_{IO_2} < 200$
- Normal LA pressure or wedge pressure < 18 mmHg

Presentation

Dyspnea and tachypnea, usually in a critically ill patient.

Diagnosis

- Physical exam: Crackles are often heard on auscultation.
- Chest X-ray: May appear normal at onset, but eventually progresses to diffuse, symmetrical interstitial and alveolar edema. Air bronchograms may be visible (see Figure 10-30).
- Pulmonary function testing: Not usually performed, but would see a restrictive pattern with a reduced Dlco.
- Arterial blood gas testing: Hypoxemia and hypocapnia, with a large AaDo2. Supplemental O_2 may not increase Po_2 greatly due to shunt.
- $Po_2/Fio2 < 200$ mmHg in ARDS.
- Pulmonary capillary wedge pressure is normal.

Pathology

Damage to type I alveolar epithelial cells, with hyperplasia of type II cells. Interstitial and alveolar fluid is present, with an inflammatory cell infiltrate. Areas of alveolar collapse. **Hyaline membranes**; fibrosis, and changes in the pulmonary vasculature can also be seen (see Figure 10-31).

Treatment

Treat the underlying cause of ARDS. Patients are typically intubated, mechanically ventilated using low-volume ventilation, and managed in an ICU.

Prognosis

High mortality (30%–50%), largely due to the underlying cause rather than the pulmonary effects of ARDS. In patients who recover, long-term respiratory sequelae are often minor.

Neonatal Respiratory Distress Syndrome

The most common cause of respiratory failure in newborns, and the most common cause of death in premature infants. It results from a deficiency of surfactant, due to immaturity of the lung. The decreased surfactant leads to atelectasis due to increased surface tension in the air–liquid interface, V/Q

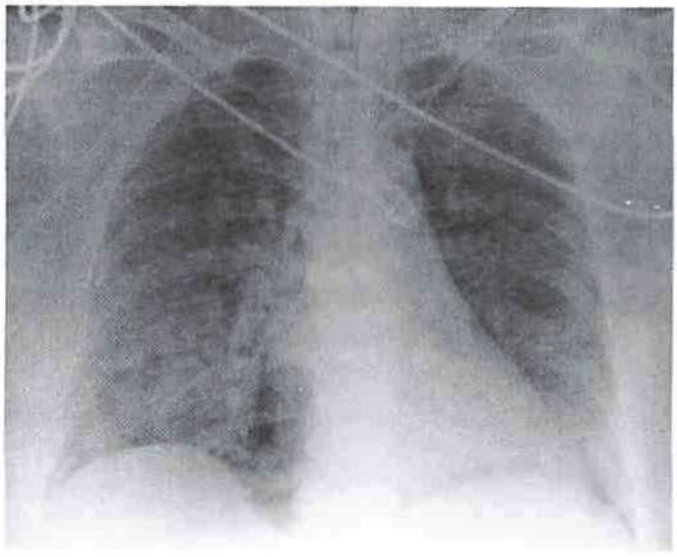


FIGURE 10-30. Chest X-ray of a patient with ARDS. Diffuse, bilateral interstitial and alveolar infiltrates are seen. (Reproduced, with permission, from Kasper DL, Braunwald E, et al. *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 1593.)

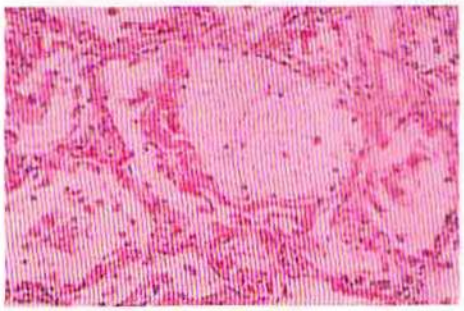


FIGURE 10-31. Alveolar damage in ARDS. The alveoli are congested and edematous, and the classic hyaline membrane can be seen. (Courtesy of the Uniformed Services University of the Health Sciences.)

mismatch, and shunting. Predisposing factors include prematurity, maternal diabetes mellitus (DM), and delivery by cesarean section.

Presentation

- Dyspnea and tachypnea

Diagnosis

- Physical exam: Infants may appear cyanotic, and crackles can be heard on auscultation.
- Fetal pulmonary maturity can be assessed by measuring the ratio of surfactant lecithin to sphingomyelin in the amniotic fluid. A ratio of 2:1 or greater indicates lung maturity.
- Chest X-ray: Low lung volumes, diffuse ground-glass appearance with air bronchograms.
- Arterial blood gas testing: Hypoxemia, hypocapnia, with a large $AaDo_2$. Hypoxemia that is refractory to supplemental O_2 due to shunting.
- Pathology: Lungs are heavier than normal, with alternating atelectatic areas and dilated alveoli. The pulmonary vessels are engorged, with leakage of fluid into the alveoli. Hyaline membranes are also seen.

Treatment

Exogenous surfactant administration. Mechanical ventilation with PEEP. Inhaled nitric oxide. Antenatal maternal corticosteroid therapy to promote lung maturity.

Prognosis

Bronchopulmonary dysplasia can develop due to treatment with high-concentration O_2 and mechanical ventilation. May be associated with PDA, intraventricular hemorrhage, and necrotizing enterocolitis.

Pneumoconiosis

A group of interstitial lung diseases caused by the inhalation of inorganic and organic dusts. This produces varying degrees of pulmonary fibrosis, with accompanying decreased compliance, reduced lung volumes, and destruction of the alveolar–capillary interface, leading to V/Q mismatch and hypoxemia. Four common inorganic pneumoconioses are:

- Silicosis: Seen in sandblasters, rock miners, quarry workers, and stonecutters.
- Coal worker's pneumoconiosis: Due to inhalation of coal dust, which contains both silica and carbon.

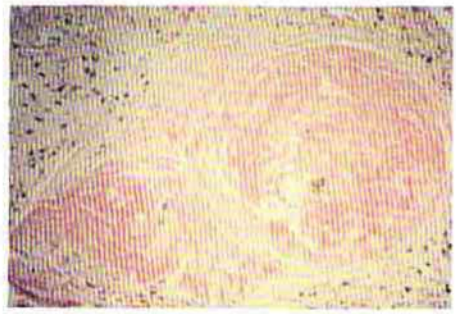


FIGURE 10-32. Silicotic nodule. Silica dust is engulfed by macrophages, initiating an inflammatory response. Concentric areas of acellular fibrosis are seen. (Courtesy of the Uniformed Services University of the Health Sciences.)

- Asbestosis: Due to inhalation of asbestos fibers. Seen in insulation, shipyard, and construction workers, as well as mechanics.
- Berylliosis: Inhalation of the metal dust beryllium. Seen in workers in aerospace, nuclear weapons, and electronics industries.

Presentation

- Dyspnea, especially with exertion.

Diagnosis

- Physical exam: Bibasilar crackles heard on auscultation. Clubbing may also be seen.
- Chest X-ray: Nodular opacities seen in silicosis, coal worker's pneumoconiosis, and berylliosis. A more linear pattern is seen in asbestosis. Calcified pleural plaques are also seen in asbestosis.
- Pulmonary function testing: Decreased TLC, FRC, RV, FEV_1 and FVC, with a normal or increased FEV_1:FVC ratio. Dlco is also decreased.
- Arterial blood gas testing: Hypoxemia, often with normo- or hypocapnia.
- Pathology: See Figures 10-32, 10-33, and 10-34.
- Berylliosis: Granulomas form due to cellular immune reaction to the beryllium.

Treatment

Avoid further exposure. No curative treatment.



FIGURE 10-33. Coal macule. Black, non-fibrotic coal macule seen in a patient with coal worker's pneumoconiosis. The macule is a collection of coal dust surrounded by little tissue reaction. Small areas of focal emphysema may also be seen. (Courtesy of the Uniformed Services University of the Health Sciences.)

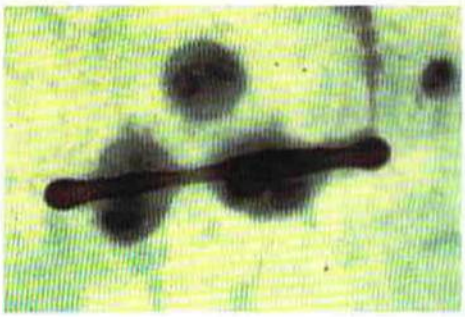


FIGURE 10-34. Ferruginous body. Prussian blue stain of a ferruginous body in a patient with asbestosis. The asbestos fibers are taken up by alveolar macrophages, leading to diffuse interstitial fibrosis, forming ferruginous bodies. These are yellow-brown, rod-shaped bodies with clubbed ends, which stain positively with Prussian blue. Dense, hyalinized, fibrocalcific plaques are seen on the parietal pleura.(Courtesy of the Uniformed Services University of the Health Sciences.)

Prognosis

- Silicosis: Associated with increased susceptibility to TB.
- Coal worker's pneumoconiosis: Simple CWP often inconsequential. If CWP leads to progressive massive fibrosis, it can lead to bronchiectasis, pulmonary hypertension, and death from respiratory failure or right-sided heart failure.
- Asbestosis: Predisposes to bronchogenic carcinoma and, less commonly, malignant mesothelioma of the pleura or peritoneum. Cancer risk increased greatly by cigarette smoking.
- Berylliosis: Can mimic sarcoidosis, with granulomas in multiple organ systems.

RESTRICTIVE LUNG DISEASES OF UNKNOWN ETIOLOGY

Includes many disorders of unclear origins that lead to pulmonary fibrosis. About 65% of patients with interstitial lung disease fall into this category. Includes sarcoidosis, Goodpasture's disease, Wegener's granulomatosis, idiopathic pulmonary fibrosis, and chronic eosinophilic pneumonia.

Sarcoidosis

Characterized by noncaseating granulomas, often involving multiple organ systems.

Presentation

More common in women and African Americans. Presents in young adulthood. Most often discovered incidentally on chest X-ray. Can present with dyspnea or nonproductive cough. Less often, presents with extrapulmonary symptoms.

Diagnosis

- Chest X-ray: Bilateral hilar lymphadenopathy, diffuse reticular densities. Divided into four stages based on chest X-ray and CT findings:
  - Stage 1: Hilar lymphadenopathy.
  - Stage 2: Hilar lymphadenopathy and interstitial changes.
  - Stage 3: No lymphadenopathy, only interstitial changes.
  - Stage 4: Pulmonary fibrosis.

- Reduced sensitivity/anergy to skin test antigens.
- Laboratory findings: Hypercalcemia (due to increased 1,25-OH vitamin D production by activated macrophages), hypercalciuria, hypergammaglobulinemia, increased ACE activity.
- Biopsy showing noncaseating granulomas in the lung with a negative microbiology work-up is highly suggestive (see Figure 10-35). Granulomas often seen in multiple organs.

Treatment

Many patients do not need treatment. Criteria for receiving treatment include impaired pulmonary function or worsening radiologic findings, systemic symptoms that interfere with activities of daily living, ocular disease, heart disease, and hypercalcemia. Treatment consists of systemic corticosteroids or other immunosuppressive drugs.

Prognosis

Natural history is very variable. In some patients, clinical and radiographic manifestations resolve spontaneously. In others, symptoms persist without progression. In a small minority, the disease progresses to widespread pulmonary fibrosis.

Idiopathic Pulmonary Fibrosis

Presentation

Insidious onset, often between 50 and 70 years of age. Dyspnea.

Diagnosis

- Physical exam: Dry crackles or rales on auscultation, clubbing.
- Chest X-ray: Diffuse, interstitial pattern bilaterally. Seen more at the bases and peripheral portions of the lung (see Figure 10-36).
- Biopsy: Definitive diagnosis, shows chronic inflammation and fibrosis of the alveolar walls.

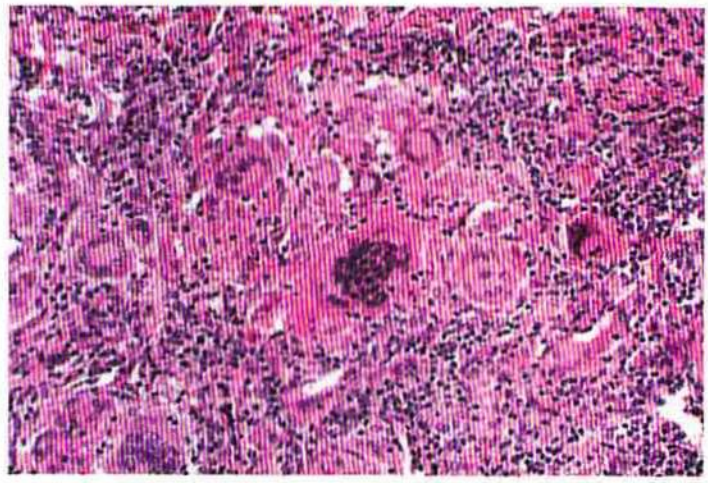


FIGURE 10-35. Photomicrograph from a patient with sarcoidosis. Noncaseating granulomas and a multinucleated giant cell are seen. (Image courtesy of PEIR Digital Library [http://peir.net].)

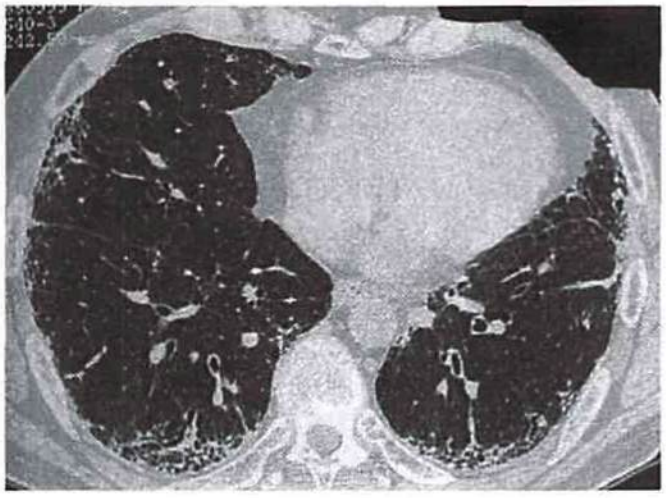


FIGURE 10-36. CT of a patient with idiopathic pulmonary fibrosis. Image demonstrates bibasilar reticular abnormalities with traction bronchiectasis and honeycombing. (Reproduced, with permission, from Kasper DL, Braunwald E, et al. *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 1556.)

Treatment

Systemic corticosteroids and other immunosuppressive drugs are used, but are not very effective. Lung transplantation may be an option for younger patients.

Prognosis

Rapid disease progression, with a mean survival of 2–5 years.

Goodpasture's Syndrome

Presentation

Pulmonary hemorrhage with concomitant kidney disease.

Diagnosis

- Anti–type IV collagen autoantibodies.
- Biopsy of kidney: Anti-GBM autoantibodies cross-react with the basement membrane of the alveolar walls.

Treatment

Plasmapheresis with or without immunosuppressive therapy to reduce the burden of anti-GBM antibodies.

Prognosis

Therapy can often control symptoms.

Wegener's Granulomatosis

Presentation

Cough, dyspnea, hemoptysis. Persistent rhinorrhea, bloody/purulent nasal discharge. Pulmonary, upper respiratory, and kidney disease.

Diagnosis

- Chest X-ray: One or several nodules, infiltrates, often with cavitation (see Figure 10-37).
- c-ANCA-positive.
  - Anti–proteinase 3 autoantibodies.
  - Biopsy: Necrotizing granulomatous vasculitis.

Treatment

Prednisone used during initial therapy. Cytotoxic agents like cyclophosphamide are also used.

Prognosis

Complete and long-term remission can often be achieved with proper treatment.

Chronic Eosinophilic Pneumonia

Presentation

Presents over weeks to months, with fever, weight loss, dyspnea, and nonproductive cough.

Diagnosis

- Chest X-ray: Peripheral pulmonary infiltrates and a pattern suggestive of alveolar filling.
- Eosinophilia.
- Pathology: Pulmonary interstitium and alveolar spaces infiltrated by eosinophils and macrophages.

Prognosis

Clinical improvement can be seen within days to weeks after therapy, typically prednisone, is initiated.

Treatment

Administration of corticosteroids.

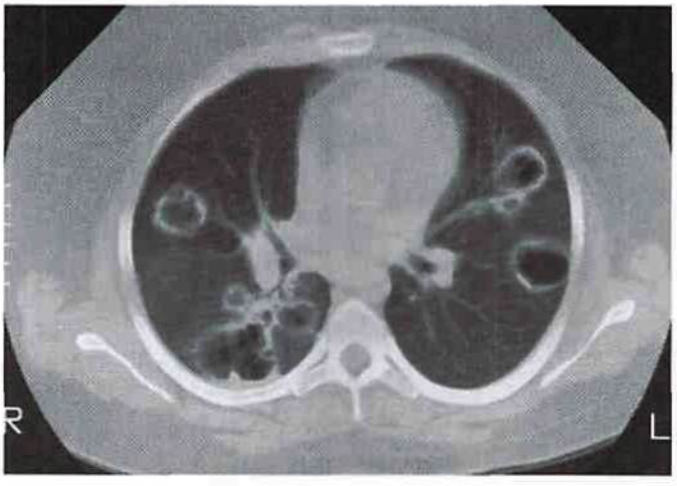


FIGURE 10-37. CT of a patient with Wegener's granulomatosis. Multiple, basilar, cavitary lesions are seen. (Reproduced, with permission, from Kasper DL, Braunwald E, et al. *Harrison's Principles of Internal Medicine*, 16th ed, New York: McGraw-Hill, 2005: 2004.)

PULMONARY VASCULAR DISEASES

The pulmonary vasculature receives the entire cardiac output and is susceptible to a number of disease processes. The two major entities discussed here are pulmonary embolism and pulmonary hypertension.

Pulmonary Embolism

Pulmonary embolism (PE) is often missed clinically and is seen in > 60% of autopsies. It occurs when a blood clot from a systemic vein lodges in one or more branches of the pulmonary artery. Most often, a PE arises from a deep vein thrombosis (DVT), but can result from embolization of tumor cells, fat, amniotic fluid, and other materials. **Virchow's triad** predisposes to thrombus formation: hypercoagulability, endothelial damage, and stasis of blood flow. Common predisposing factors include immobilization, cancer, multiple fractures, and the use of oral contraceptive pills.

Decreased perfusion with continued ventilation causes an increase in dead space following a PE. This should lead to hypercapnia, but patients often hyperventilate and may be surprisingly hypocapnic. The release of inflammatory mediators can lead to bronchoconstriction, V/Q mismatch, and hypoxemia. Reduced forward output of the right ventricle can lead to syncope or hypotension and shock.

Presentation

Tachycardia, tachypnea, dyspnea, hemoptysis, pleuritic chest pain. Syncope and hypoxemia may also be seen.

Diagnosis

- Physical exam:
  - Tachycardia and tachypnea
  - Localized crackles or wheezes, however the lung exam is often normal.
  - A pleural rub may be present.
  - With right ventricular overload, a right-sided S4 and loud P2 may be heard. JVD may also be observed.
  - Lower extremity tenderness, swelling, and a palpable clot within a vessel suggestive of a DVT may be seen.
- Chest X-ray: Usually nonspecific, including atelectasis and elevation of the hemidiaphragm. Dilation of the pulmonary artery, Hampton's hump (wedge-shaped consolidation in the lung periphery adjacent to the pleura), Westermark's sign (abrupt cut-off of pulmonary vascularity distal to a PE), or a pleural effusion may also be seen.
- CT angiography can show the filling defect due to the thrombus (see Figure 10-38).
- V/Q scan will show area of ventilation without perfusion.
- Arterial blood gas testing: Decreased Po_2, decreased Pco_2, increased pH and $AaDo_2$.

Treatment

Anticoagulation therapy, usually with IV heparin or low-molecular-weight heparin followed by oral warfarin, for 3–6 months. Thrombolytic therapy may be useful in a subset of patients with massive PE and hypotension. Placement of a filtering device in the IVC can be used in patients who cannot tolerate anticoagulation due to an elevated bleeding risk.

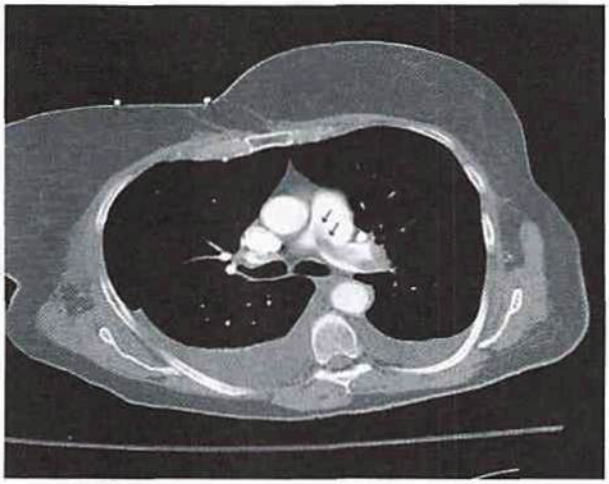


FIGURE 10-38. CT of a patient with a pulmonary embolism. Massive bilateral pulmonary arterial filling defects (arrows) can be seen. (Reproduced, with permission, from Crawford MH, *Current Diagnosis & Treatment in Cardiology*, 2nd ed, New York: McGraw-Hill, 2003: 370.)

Prognosis

Variable, ranging from sudden death to asymptomatic resolution.

Pulmonary Hypertension

Elevation of the intravascular pressure within the pulmonary circulation, often defined as a mean pulmonary artery pressure > 25 mmHg at rest or > 35 mmHg with exertion. Idiopathic pulmonary arterial hypertension (PAH) has no known cause and a poor prognosis. It occurs in the absence of underlying heart or lung disease. Secondary pulmonary hypertension is more common, and is related to lung or heart disease, including:

- Chronic thromboembolic disease.
- Loss of vessels by scarring or destruction of alveolar walls.
- Chronic hypoxemia.
- Increased flow (left-to-right shunt).
- Elevated left atrial pressure, as in CHF.

Presentation

Dyspnea and exertional fatigue. Substernal chest pain, similar to angina pectoris, is sometimes seen. Occasionally chest pain is more right-sided. If cardiac output falls enough, syncope can result.

Diagnosis

- Physical exam:
  - Lung examination often normal unless pulmonary hypertension is due to concomitant lung disease.
  - Loud P2, right-sided S3 and S4.
  - JVD.
  - Right ventricular heave.
- Chest X-ray: Increased prominence and size of hilar pulmonary arteries, which rapidly taper off. Enlarged cardiac silhouette (particularly RV and RA enlargement). Redistribution of blood flow to the upper lungs (see Figure 10-39).
- Pulmonary function testing: Spirometry and lung volumes usually normal, with a decreased Dlco.

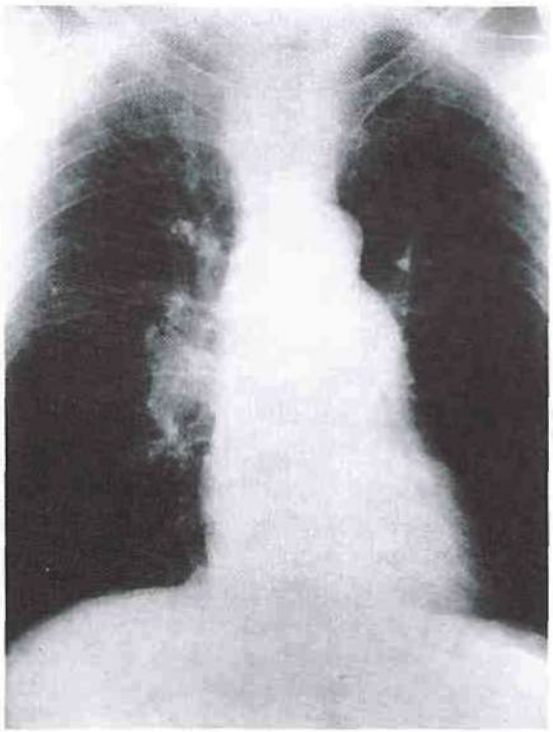


FIGURE 10-39. Chest X-ray of a patient with pulmonary hypertension. The pulmonary arteries are dilated with a lack of peripheral vasculature. (Reproduced, with permission, from Crawford MH, *Current Diagnosis & Treatment in Cardiology*, 2nd ed, New York: McGraw-Hill, 2003: 387.)

- Arterial blood gas testing: Useful in determining whether hypoxemia or acidosis plays a role in the disease's etiology.
- Pathology: Intimal hyperplasia and medial hypertrophy of small arteries and arterioles, leading to obliteration of the lumen. Plexogenic lesions are typically seen in idiopathic disease. Thickening of the walls of larger arteries is also seen. Right ventricular hypertrophy is also a feature.

TREATMENT

Supplemental O_2 therapy, various vasodilators (i.e., sildenafil, endothelin receptor antagonists, or prostacyclins), inhaled nitric oxide, and anticoagulation therapy.

PROGNOSIS

Right-sided heart failure can occur due to elevated right-sided pressures.

- Idiopathic PAH: Poor prognosis, often resulting in death within a few years of diagnosis if untreated.
- Secondary pulmonary hypertension: Mainstay of therapy is treatment of the underlying disease.

KEY FACT

Pulmonary edema is an intra-alveolar accumulation of fluid. It can be caused by increased hydrostatic pressure (i.e., LV failure), increased capillary permeability (i.e., ARDS), or several other mechanisms (i.e., high altitude, neurologic injury, or opiate overdose).

LUNG CANCER

Metastatic disease is more common than primary tumors. Bronchogenic carcinoma, the main type of primary lung tumor, is the leading cause of cancer-related death in both men and women, and is closely linked with cigarette smoking. Cigarette smoking is clearly related to certain subtypes of lung cancer. Quitting reduces subsequent risk of developing lung cancer, but this risk

likely never drops to that of a nonsmoker. Occupational exposures can predispose to lung cancer, including: asbestos (mesothelioma and bronchogenic carcinoma), arsenic, haloethers, and polycyclic aromatic hydrocarbons.

Areas of parenchymal scarring can serve as foci for the development of adenocarcinoma and, more specifically, bronchoioalveolar carcinoma. Most of the respiratory symptoms seen with lung cancer are due to local tissue destruction due to tumor growth or airway obstruction.

Presentation

An endobronchial tumor can present with cough and hemoptysis. Postobstructive pneumonia and dyspnea develop due to tumor obstructing an airway. A pleural effusion and chest pain can result from pleural involvement. Anorexia and weight loss is also seen.

- Superior vena cava syndrome: Compression of the vena cava by tumor leads to facial swelling, cyanosis, and dilation of the veins of the head, neck, and upper extremities.
- Pancoast tumor at apex of the lung: Can present with Horner's syndrome (ptosis, miosis, and anhidrosis) due to involvement of the cervical sympathetic plexus.
- Hoarseness due to paralysis of the recurrent laryngeal nerve.
- Paraneoplastic endocrine syndromes include:
  - ACTH or ACTH-like activity with small cell carcinoma.
  - SIADH with small cell carcinoma.
  - PTH-like activity with squamous cell carcinoma.
- Distant metastases to the brain, bone, liver, or adrenals can present with organ-specific symptoms.

Diagnosis

- Chest X-ray: Nodule or mass within the lung. Centrally located: Squamous and small cell. Peripherally located: Adenocarcinoma and large cell. Involvement of the hilar lymph nodes or pleura can also be seen.
  - An exception to this is the bronchioloalveolar subtype of adenocarcinoma, which often has a more diffuse radiographic appearance, termed **ground-glass opacity**, similar to pneumonia.
- CT or PET scans used to determine location, lymph node involvement, or metastasis for staging.
- Cytologic examination of sputum or washings from a bronchoscopy, or tissue pathology from a lung biopsy.
- Pulmonary function testing is often used to assess whether a patient has the residual capacity to survive surgical resection of a tumor.
- Pathology:
  - Non-small cell lung cancer
    - Squamous cell carcinoma
      - One-third of all bronchogenic carcinomas.
      - Characterized by the presence of **keratin pearls**.
      - Tends to be localized in the large, proximal airways.
      - May cavitate.
    - Adenocarcinoma
      - Most common type of bronchogenic carcinoma.
      - Often arises in the lung periphery or at sites of scarring.
      - Malignant cells may form glands and secrete mucus.
      - Bronchioloalveolar subtype: Not clearly related to smoking, and spreads along and lines alveolar walls.

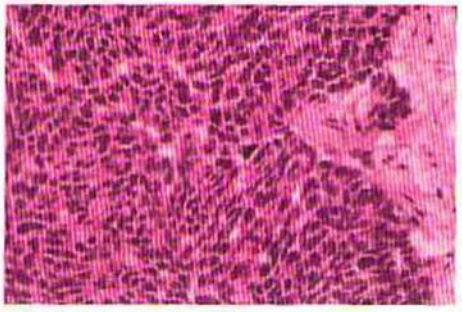


FIGURE 10-40. Photomicrograph of a patient with small cell carcinoma. The cells are small, with little cytoplasm or other defining characteristics. (Courtesy of the Uniformed Services University of the Health Sciences.)

- Large cell carcinoma
  - 15%–20% of bronchogenic carcinomas.
  - Undifferentiated tumor.
  - Arises in the lung periphery.
- Small cell lung cancer
  - 20% of all bronchogenic carcinomas.
  - Malignant cells appear as small, darkly stained cells with scant cytoplasm (see Figure 10-40).
  - Generally arises in the proximal airways.
  - Commonly produces polypeptide hormones such as ACTH and ADH.

TREATMENT

- **Small cell carcinoma:** Metastases occur very early in the disease course, so surgery is not an option, only chemotherapy and/or radiation.
- **Non–small cell carcinoma:** Surgical resection if there is no distant spread. If metastases are present, then chemotherapy and/or radiation.

PROGNOSIS

Overall 5-year survival is about 14%. Squamous cell carcinoma has the best prognosis, while small cell carcinoma has the worst. Early-stage disease, while rarely found, has a much better prognosis than late-stage disease.

PULMONARY INFECTIONS

Pneumonia

Infection of lung parenchyma is a major cause of morbidity and mortality, accounting for nearly 10% of all hospital admissions and for approximately 80,000 deaths in the United States each year.

Infectious causes include bacterial, viral, mycoplasmal, and mycobacterial pathogens, the most common being *Streptococcus pneumoniae* (see Table 10-10). Risk factors include viral URI, alcohol abuse, cigarette smoking, and COPD. Infection can spread to the lungs by inhalation, aspiration, and hematogenous spread from other sites. Inflammation and infection of the distal air spaces leads to a reduction in ventilation to those areas. If perfusion is maintained, then V/Q mismatch results, with or without shunting.

TABLE 10-10. Common Causes of Pneumonia

ORGANISM	CHARACTERISTICS	COMPLICATIONS	TREATMENT
Streptococcus pneumoniae	Gram-positive diplococci; community-acquired; most common in elderly or debilitated persons; **lobar pneumonia.**	Empyema.	Penicillins, cephalosporins, macrolides, some quinolones.
Staphylococcus aureus	Gram-positive cocci in clusters; often a complication of influenza, viral pneumonias, or blood-borne infection in IV drug users; seen in hospitalized patients, the elderly, and those with chronic lung disease; **bronchopneumonia.**	Abscess formation or empyema not uncommon; bacterial endocarditis and brain and kidney abscesses possible from hematogenous spread.	Oxacillin, nafcillin, vancomycin (MRSA), linezolid.
Haemophilus influenzae	Gram-positive coccobacillus; usually seen in infants and children, but may occur in adults with COPD; **bronchopneumonia.**	Meningitis and epiglottitis in infants and children.	Second- or third-generation cephalosporins, trimethoprim-sulfamethoxazole.
Klebsiella pneumoniae	Gram-positive rod; most frequent in diabetic or alcoholic patients; high mortality rate in the elderly; **currant-jelly sputum; bronchopneumonia.**	Large amount of damage to the alveolar walls leading to necrosis and abscess formation.	Aminoglycosides, third-generation cephalosporins.
Pseudomonas aeruginosa	Gram-positive rod; appears blue-green when cultured; common cause of nosocomial pneumonia and pneumonia in immunocompromised and CF patients.	Focal hemorrhage and necrosis.	Combination therapy using ticarcillin, piperacillin, ciprofloxacin, cefepime, or gentamicin.
Legionella pneumophila	Gram-positive bacillus, but stains poorly; infection spreads by inhalation of aerosol from contaminated water; affects both healthy and debilitated adults; **often lobar, but no characteristic pattern.**	Relatively high mortality rate if untreated.	Macrolide, quinolone.
Anaerobes	Due to aspiration of secretions from the oropharynx into the tracheobronchial tree; patients with impaired consciousness or difficulty swallowing are at highest risk; often located in dependent segments of lung.	Abscess or empyema formation is common.	Penicillin, clindamycin.
Mycoplasma	Frequent cause of **interstitial pneumonia** in young adults; insidious onset with mild, limited course; associated with **nonspecific cold agglutinins.**		Macrolide, quinolone.

TABLE 10-10. Common Causes of Pneumonia *(continued)*

Organism	Characteristics	Complications	Treatment
Viral pneumonia	Most common pneumonia of childhood. Caused by influenza viruses, adenoviruses, rhinovirus, and RSV; measles virus produces giant cell pneumonia.		▪ Influenza A: Amantadine and rimantadine. ▪ Influenza A and B: Zanamivir and oseltamivir.
Coxiella burnetii	Rickettsial organism; infects people working with cattle or sheep, or those who drink unpasteurized milk from infected animals; interstitial pneumonia.	Can cause hepatitis or myocarditis.	Doxycycline.
Pneumocystis jiroveci (formerly *Pneumocystis carinii*)	Usually classified as a protozoan; identified on silver stain; is the most common opportunistic infection in AIDS patients; **ground-glass opacities** on CT.		Trimethoprim-sulfamethoxazole.

Presentation

Fever (+/– chills), cough (+/– sputum production), and dyspnea. A non-productive cough suggests viral or mycoplasmal pneumonia. Blood-tinged or rusty sputum suggests bacterial pneumonia. Pleuritic chest pain due to inflammation adjacent to the pleura.

Diagnosis

- Physical exam:
  - Tachycardia, tachypnea, and fever.
  - Crackles over the affected area on auscultation.
  - Bronchial breath sounds, increased fremitus, and egophony.
  - Dullness to percussion if there is frank consolidation or associated effusion.
- Laboratory tests: Leukocytosis with left shift (increased PMN fraction of WBCs) and increased bands (immature WBCs) in bacterial pneumonia.
- Chest X-ray: Allows classification of the distribution of the infection into lobar, patchy, or interstitial pattern. Pleural effusions may accompany a bacterial pneumonia.
  - Lobar pneumonia: Infection tends to spread through the entire lobe, with intra-alveolar exudates. *Streptococcus pneumoniae* is the classic pathogen (see Figure 10-41).
  - Bronchopneumonia: Patchy distribution involving more than one lobe, with distal airway inflammation and alveolar disease. Caused by a wide variety of organisms.
  - Interstitial (atypical) pneumonia: Diffuse, patchy inflammation of the interstitial walls (see Figure 10-42).
- Sputum Gram's stain and culture. *Mycoplasma*, *Chlamydia*, and *Legionella* require additional serology and antigen testing.
- Nasal swab
- Arterial blood gas testing: Reduced Pao_2 with normal or reduced $Paco_2$ due to hyperventilation.

Treatment

Antibiotic therapy is the mainstay for bacterial pneumonia (see Table 10-9). Supportive care for most viral pneumonias. Antivirals available for influenza infection.



FIGURE 10-41. Lobar pneumonia. Chest X-ray of a 34-year-old patient with lobar pneumonia. Air bronchograms can be seen within the area of consolidation. (Image courtesy of PEIR Digital Library [http://peir.net].)

Prognosis

In most cases, complete recovery without long-term sequelae. Complications include:

- Lung abscess: Pus collection, often caused by bacterial pneumonia, bronchial obstruction, or aspiration. Often due to *Staphylococcus*, *Pseudomonas*, *Klebsiella*, *Proteus*, or anaerobic organisms. Requires antibiotics and drainage.
- Empyema: Pus in the pleural space. Often caused by anaerobes and staphylococci. Requires drainage.

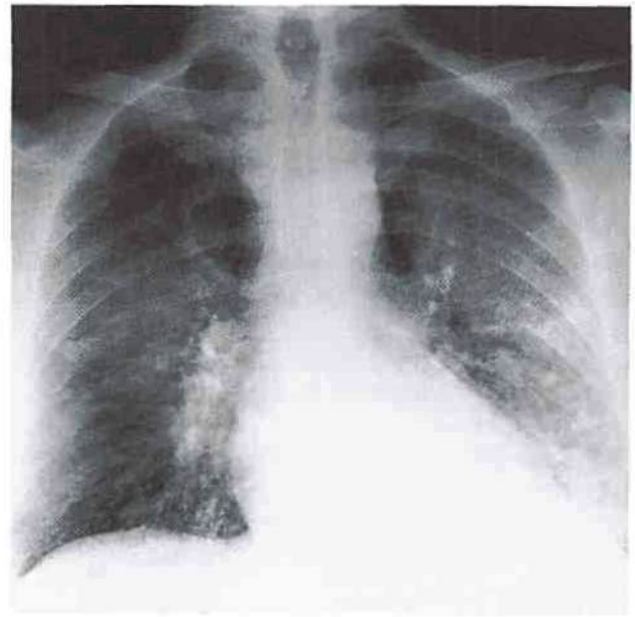


FIGURE 10-42. Interstitial pneumonia. Chest X-ray of a patient with mycoplasmal pneumonia. Diffuse interstitial and alveolar infiltrates can be seen. (Reproduced, with permission, from Hall JB, Schmidt GA, Wood LDH, *Principles of Critical Care*, 3rd ed, New York: McGraw-Hill, 2005: 826.)

Tuberculosis

Approximately one-third of the world's population has been infected with TB, and there are 2–3 million deaths due to TB each year. Burden of disease is greatest in developing countries. Caused by *Mycobacterium tuberculosis*, an aerobic, rod-shaped, acid-fast bacterium (termed "red snappers"), which is transmitted by airborne droplets from infected patients. There are two forms of TB, primary and secondary.

- **Primary TB:** At initial infection, Ghon's complexes develop (peripheral subpleural parenchymal lesion and involved hilar lymph nodes). Caseating granuloma with multinucleated giant cells due to delayed hypersensitivity reaction.
- **Secondary (reactivation) TB:** Results from reactivation of a prior site of infection. Lesions localized to the lung apices with hilar lymph node involvement. Granulomatous lesions form and rupture, resulting in cavitary lesions. Scarring and calcification may be seen.

Presentation

Pulmonary symptoms include productive cough and hemoptysis. Respiratory function is generally well preserved, perhaps because of localization of the destructive disease to the apices. Systemic symptoms include weight loss, fever, and night sweats.

Diagnosis

- Physical exam:
  - Weight loss and wasting.
  - Crackles over the affected area on auscultation.
- Tuberculin skin test (PPD): Acts through a type IV hypersensitivity reaction. A small amount of protein from the organism is injected under the skin. Induration or swelling at the site after 48–72 hours indicates prior exposure to TB. This does not differentiate between active and prior infections.

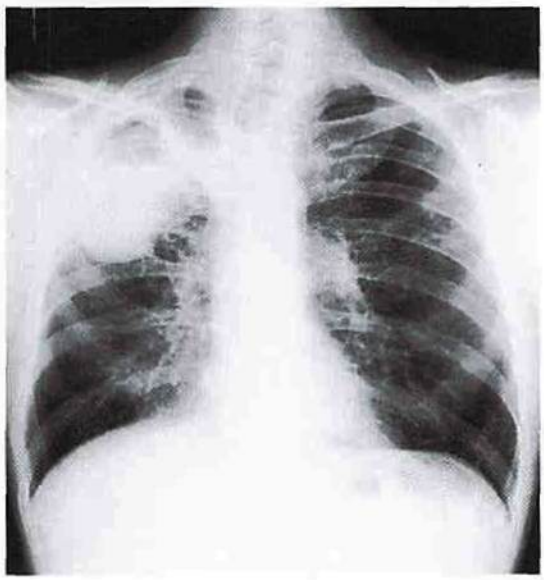


FIGURE 10-43. Tuberculosis. Chest X-ray of a patient with reactivation TB, hilar lymphadenopathy, and a cavitary lesion in the right upper lobe. (Reproduced, with permission, from Doherty GM, Way LW, *Current Surgical Diagnosis & Treatment*, 12th ed, New York: McGraw-Hill, 2006: 371.)

CLINICAL CORRELATION

The major side effects of **isoniazid** are hepatotoxicity, peripheral neuropathy, and CNS effects. The latter two are due to depletion of pyridoxine (vitamin B_6). Therefore, patients are given pyridoxine supplementation during isoniazid therapy.

- Chest X-ray:
  - **Primary TB:** Nonspecific, often lower lobe infiltrate, hilar lymph node enlargement, and pleural effusion.
  - **Secondary TB:** Lesions located in the apices or superior segment of a lower lobe. Infiltrates, cavities, nodules, scarring, and/or contraction may be seen (see Figure 10-43).
- Culture of the organism from sputum is needed for a definitive diagnosis. Acid-fast staining is useful for quicker results.

Treatment

Six months of treatment with isoniazid, pyridoxine (vitamin B_6), and rifampin, supplemented during the first 2 months by pyrazinamide and ethambutol. Isoniazid and pyridoxine alone for 9 months in individuals with a positive skin test but no active disease (latent TB).

Prognosis

Most patients with primary TB are asymptomatic. Lifetime risk of reactivation is about 10% in immunocompetent patients. This is elevated in patients with AIDS or other immunosuppressive states. Reactivation TB can be com-

TABLE 10-11. Fungal Infections of the Lungs

Organism	Presentation	Characteristics	Treatment
Candida albicans	Fever, tachypnea, patchy infiltrates on chest X-ray.	Uncommon cause of pneumonia; hematogenous spread seen in immunocompromised patients.	Amphotericin B and fluconazole.
Cryptococcus neoformans	Often asymptomatic, but can have productive cough, fever, weight loss.	Can also produce cryptococcal meningitis; organism's encapsulated appearance can be seen with India ink stain.	Amphotericin B plus flucytosine.
Aspergillus	Wheezing, dyspnea, and cough with allergic bronchopulmonary aspergillosis; fever, cough, dyspnea, pleuritic chest pain, and hemoptysis seen in invasive forms, usually in immunocompromised patients.	Fungal balls (aspergillomas) can form in pre-existing cavities; the invasive form of aspergillosis has a tendency to grow into vessels with widespread hematogenous dissemination; seen as branching hyphae in tissue.	Amphotericin B or itraconazole.
Blastomyces dermatitidis	Fever, chills, productive cough.	Found in the midwestern and southeastern United States.; broad-based budding yeast.	Amphotericin B or itraconazole.
Histoplasma capsulatum	Often asymptomatic; the young or immunocompromised may have disseminated or chronic disease with fever, fatigue, and weight loss.	Found in the river valleys of the central United States, and in soil contaminated by bird droppings; elicits caseating granuloma formation in tissue; the disseminated form is marked by multi-system involvement with infiltrates of macrophages filled with fungus; round or oval yeast forms in tissue.	Amphotericin B +/– itraconazole.
Coccidioides immitis	Fever, cough, headache, chest pain; disseminated or chronic disease produces systemic symptoms.	Found in the southwestern United States, Mexico, and South America; may have acute, disseminated, or chronic course. Fungal spherules containing endospores are found within granulomas.	Amphotericin B; surgery may also have a role.

plicated by miliary TB, in which distal organs are seeded with innumerable small lesions. Extrapulmonary TB includes: tuberculous meningitis, Potts' disease of the spine, psoas abscess, and paravertebral abscess.

Fungal Infections

A variety of fungal pathogens can cause pulmonary infection (see Table 10-11).

Pharmacology

DRUGS TO TREAT DISORDERS OF RESPIRATION

Albuterol, Isoproterenol, Terbutaline

Mechanism

Inhibits mast cell and monocyte release of TNF-α. Site of action is smooth muscle as β_2-adrenoceptor agonists.

Uses

Acute asthma by relaxing bronchial smooth muscle via β2 agonism. Short-acting bronchodilators are used for acute asthma exacerbations. Albuterol (most commonly used in acute exacerbations), terbutaline (for status asthmaticus), isoproterenol (nonspecific, relaxes bronchial smooth muscle).

Side Effects

Hypertension, angina, vomiting, vertigo, CNS stimulation, unusual taste, and drying or irritation of the oropharynx.

Salmeterol

Mechanism

Activates β_2-selective receptors for asthma prophylaxis. Salmeterol relaxes and opens air passages in the lungs.

Uses

Long-acting prophylaxis against asthma and COPD.

Side Effects

Coughing, tremor, arrhythmia, chest pain, headache, and hives.

Theophylline, Theobromine, Caffeine

Mechanism

Inhibits phosphodiesterase isoenzymes, decreases cAMP hydrolysis, increases cAMP, and causes bronchodilation. Site of action is smooth muscle.

Uses

Bronchodilator used to relieve airflow obstruction in acute asthma and to reduce the severity of symptoms.

Side Effects

Cardiotoxicity and neurotoxicity.

Ipratropium

Mechanism

Competitively blocks muscarinic acetylcholine M_2 receptors, increases acetylcholine release, preventing bronchoconstriction.

Uses

Asthma, chronic obstructive airway disease, bronchial constriction.

Side Effects

Dry mouth due to effects on salivary glands, drying of bronchial secretions with difficulty with expectoration, glaucoma, and acute urinary retention.

Cromolyn, Nedocromil

Mechanism

Prevents release of mediators from mast cells and alters function of delayed chloride channels in the cell membrane, inhibiting cellular activation (see Figure 10-44 and Table 10-12).

Uses

Antigen- and exercise-induced asthma. Cromolyn and nedocromil are effective only for prophylaxis of asthma, but are not effective during an acute asthma attack.

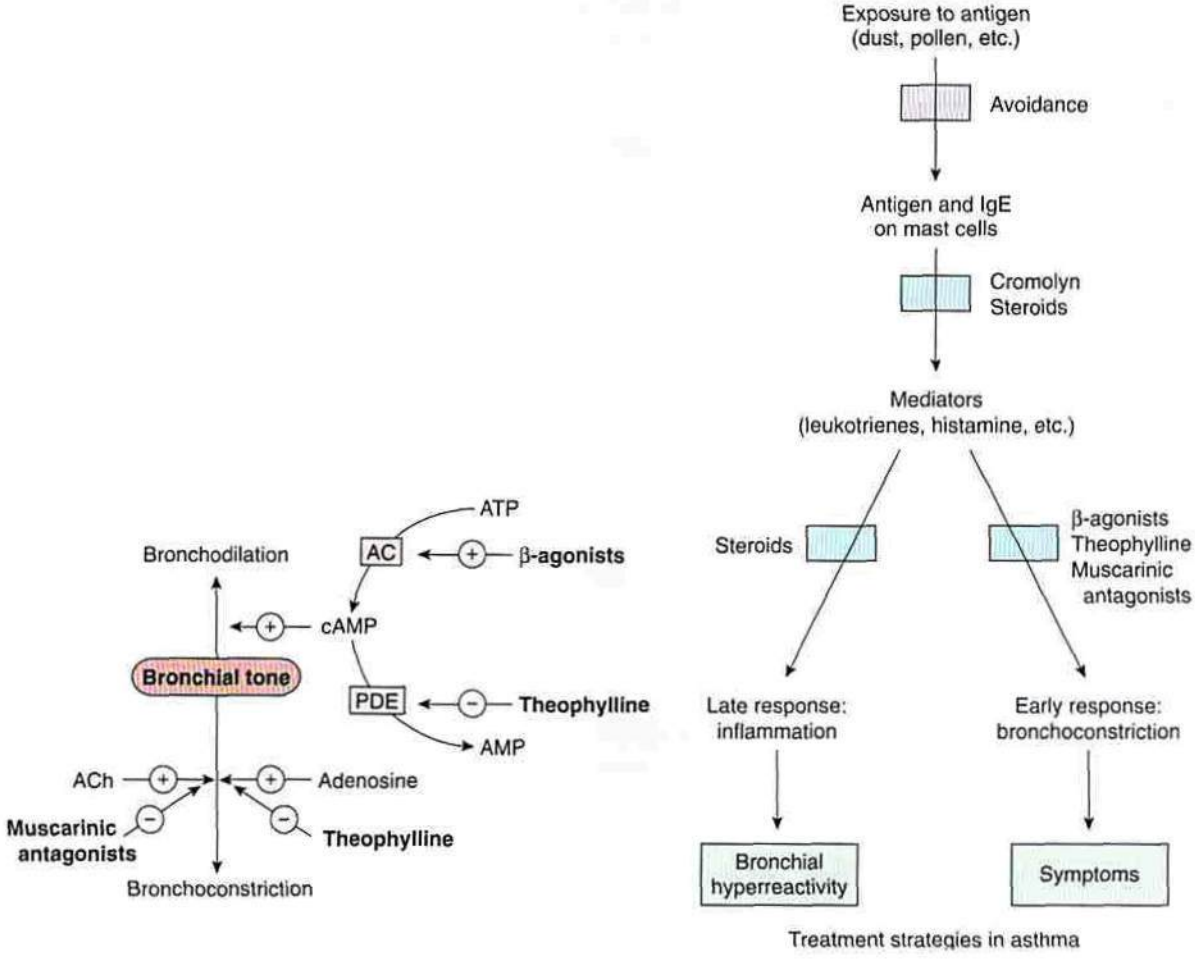


FIGURE 10-44. Site of action for cromolyn, corticosteroids, and antileukotrienes. (Modified, with permission, from Katzung BG, Trevor AJ, Pharmacology: Examination and Board Review, 5th ed, Stamford, CT: Appleton & Lange, 1998: 159 and 161. Copyright © McGraw-Hill.)

TABLE 10-12. Common Pharmatherapeutics in the Treatment of Asthma

Drug Class	Specific Drug
Nonspecific β-agonists	Isoproterenol—relaxes bronchial smooth muscle (β_2). Adverse effect is tachycardia (β_1).
β_2 agonists	Albuterol—relaxes bronchial smooth muscle (β_2). Use during acute exacerbation. Salmeterol—long-acting agent for prophylaxis. Adverse effects are tremor and arrhythmia.
Methylxanthines	Theophylline—likely causes bronchodilation by inhibiting phosphodiesterase, thereby ↓ cAMP hydrolysis. Usage is limited because of narrow therapeutic index (cardiotoxicity, neurotoxicity).
Muscarinic antagonists	Ipratropium—competitive block of muscarinic receptors, preventing bronchoconstriction.
Cromolyn	Prevents release of mediators from mast cells. Effective only for the prophylaxis of asthma. Not effective during an acute asthmatic attack. Toxicity is rare.
Corticosteroids	Beclomethasone, prednisone—inhibit the synthesis of virtually all cytokines. Inactivate NF-κB, the transcription factor that induces the production of TNF-α, among other inflammatory agents. 1st-line therapy for chronic asthma.
Antileukotrienes	Zileuton—A 5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes. Zafirlukast, montelukast—block leukotriene receptors. Especially good for aspirin-induced asthma.

Side Effects

Toxicity is rare because cromolyn is so poorly absorbed. Some adverse reactions include throat irritation, cough, mouth dryness, chest tightness, and wheezing.

Montelukast, Zafirlukast

Mechanism

Blocks cysteinyl-leukotriene (LT) receptor, LTD_4-receptor antagonist.

Uses

Effective in blocking airway responses and relaxing airways.

Side Effects

Unusual weakness, headaches, nausea, GI disturbances, liver toxicity. A rare side effect is pus in the urine.

Zileuton

Mechanism

Blocks 5-lipoxygenase which converts arachidonic acid to leukotrienes.

Uses

Blocked airway responses to exercise and to antigen challenge in mild-to-moderate asthma.

Side Effects

Elevated liver function tests, headache, upset stomach, heartburn, vomiting, and constipation.

Prednisone (Oral), Beclomethasone (Inhaled)

Mechanism

Decreases formation of cytokines, inactivates nuclear factor-κB, the transcription factor that induces the production of TNF-α inhibits generation of vasodilators, decreases microvascular permeability, and reduces mediator release from eosinophils.

Uses

Chronic asthma.

Side Effects

Vision problems, eye pain, sore throat, seizures, depression, loss of contact with reality, confusion, muscle twitching, shaking, difficulty falling asleep or staying asleep, increasing the rate of osteoporosis, and bulging eyes.

DRUGS FOR ALLERGY

First-Generation Histamine Blockers: Diphenhydramine, Dimenhydrinate, Chlorpheniramine

Mechanism

Reversibly inhibits H_1 histamine receptors.

Uses

Allergic reactions (such as rhinitis and urticaria), motion sickness, and sleep aid.

Side Effects

Low blood pressure, palpitations, increased heart rate, sedation, tiredness, sleepiness, dizziness, disturbed coordination, antimuscarinic, anti-β adrenergic.

Second-Generation Histamine Blockers: Loratadine, Fexofenadine, Desloratadine

Mechanism

Reversibly inhibits H_1 histamine receptors.

Uses

Antihistamine that provides relief of seasonal allergy symptoms such as watery eyes, rhinitis, itching eyes, and sneezing.

Side Effects

Headache, fatigue, dry mouth, thirst, dry nose, nervousness, rapid heartbeat, diarrhea.

Codeine

Mechanism

Activates the μ-opioid receptor. Codeine is an alkaloid derived from opium.

Uses

Analgesic to relieve mild-to-moderate pain.

Side Effects

Lightheadedness, dizziness, sedation, nausea, and vomiting.

Dextromethorphan

Mechanism

Acts as an agonist at opioid receptors to modulate synaptic transmission.

Uses

Cough suppression.

Side Effects

Addiction, respiratory depression, constipation, miosis, additive CNS depression with other drugs.

Rapid Review

Key Terms

Acinus	The structure distal to the terminal bronchioles, includes the respiratory bronchiole, alveolar ducts, and alveoli.
Atelectasis	Collapse of lung spaces secondary to inadequate expansion.
Bullae	Multiple, contiguous, enlarged airspaces that range in diameter from < 0.5 mm to > 2.0 cm, sometimes forming cyst-like structures that with progressive enlargement are referred to as **bullae.**
Dyspnea	Shortness of breath or labored, difficult breathing.
Elastase/ metalloproteinase	Produced by macrophages and neutrophils during inflammation; cause tissue damage.
Exudate	A fluid collection outside the vasculature with an abundance of protein and cellular elements. When within the lung, a fluid:serum LDH ratio of > 0.6, and protein ratio of > 0.5.
Hemoptysis	Coughing up blood.
Hypercapnia	Increased CO_2 in the blood.
Hypoxemia	*Decreased O_2 in the blood.*
Paraneoplastic syndrome	A collection of signs and symptoms secondary to the release of substance from a tumor, or the body's reaction to the presence of a tumor.
Perfusion	The flow of blood to an organ or tissue.
Pneumonia	Generic term for infection of the lung.
Reid index	*The magnitude of the increase in size of the mucus-secreting glands is assessed by the ratio of the thickness of* the submucosal gland layer to that of the bronchial wall.
Transudate	A fluid collection outside the vasculature with an absence of protein and cellular elements. When within the lung, fluid:serum LDH ratio of < 0.6 and protein ratio of < 0.5.
Ventilation	The exchange of air between the lungs and the atmosphere.

ATELECTASIS

Alveolar collapse. Is usually reversible and should be treated quickly to prevent hypoxemia and infection of the collapsed lung.

- **Ventilation-perfusion imbalance:** Shunting of inadequately oxygenated blood from pulmonary arteries into veins, causing a ventilation-perfusion imbalance and hypoxia.

Resorption Atelectasis

Obstruction prevents air from reaching distal airways. The air already present gradually becomes absorbed and alveolar collapse follows.

Compression Atelectasis

Associated with accumulation of fluid, blood, or air within the pleural cavity, which mechanically collapses the adjacent lung. A frequent cause of pleural effusions is congestive heart failure. Pneumothorax also causes compression of the lung.

Microatelectasis

Generalized loss of lung expansion caused by a complex series of events, the most important of which is loss of surfactant.

Contraction Atelectasis

Occurs when local or generalized fibrotic changes in the lung or pleura inhibit expansion and increase elastic recoil during inspiration.

OBSTRUCTIVE LUNG DISEASE

Characterized by limitation of airflow resulting from partial or complete obstruction at any level. Major disorders include asthma, emphysema, chronic bronchitis, bronchiectasis, cystic fibrosis, and bronchiolitis. The hallmark of obstructive disease is a decreased expiratory flow rate. The FEV_1:FVC ratio is decreased.

- **Forced vital capacity (FVC):** Volume that can be forcibly expired after a maximal inspiration.
- **Forced expiratory volume in 1 second (FEV_1).** Volume that can be expired in the first second following a maximal inspiration. Normally 80% of the FVC.

Asthma (Reactive Airway Disease)

Characterized by episodic, reversible bronchospasms due to an exaggerated bronchoconstrictor response to various stimuli (primarily persistent bronchial inflammation). Typified by an eosinophilic infiltrate. Occlusion of bronchi/bronchioles can occur in asthmatics by formation of mucus plugs containing shed epithelial cells in a swirl pattern (**Curschmann's spiral**). Mucus plugs may also contain collections of crystalloids made up of eosinophil proteins (**Charcot-Leyden crystals**).

- **Extrinsic asthma:** Episode triggered by a type 1 hypersensitivity reaction (CD4 T cells release cytokines that cause IgE formation, increased mast cell formation, and activation of eosinophils) induced by exposure to an extrinsic agent.
- **Atopic asthma:** IgE-mediated hypersensitivity. May also see skin atopy. Typically develops in the first few years of life.

- **Intrinsic asthma:** External factors trigger bronchospasm (aspirin, pulmonary infections, cold, psychological stress, exercise, and inhaled irritants). Serum IgE is normal. Develops later in life.
- **Status asthmaticus:** Prolonged, severe asthma attack in which bronchospasm does not respond to traditional treatments.

Chronic Obstructive Pulmonary Disease

Irreversible airflow obstruction (versus asthma, in which airflow obstruction is reversible). This term includes two common conditions: emphysema and chronic bronchitis. With severe COPD, the patient develops hypercapnia, hypoxia, and possibly cyanosis. The patient will ultimately develop pulmonary hypertension and cardiac failure.

Emphysema

Permanent enlargement of the airspaces beyond the terminal bronchioles accompanied by destruction of their walls. There are two categories of presentation. "**Pink puffers**" are barrel-chested, dyspneic, and have prolonged expiration. They have adequate oxygenation of hemoglobin. "**Blue bloaters**" have a history of chronic bronchitis and decreased respiratory drive (CO_2 retention); they become hypoxic and are cyanotic. Causes include decreased protease activity, α_1-antitrypsin deficiency (emphysema without smoking history), or oxidant-antioxidant imbalance.

- **Centriacinar emphysema:** Pattern of involvement is the central or proximal part of the acinus. Seen most often in people who smoke cigarettes. Affects upper lobes more severely.
- **Panacinar (panlobular) emphysema:** Acini are uniformly enlarged from the level of the respiratory bronchiole Seen most often in people with α_1-antitrypsin deficiency. Affects lower lobes more severely.
- **Distal acinar (paraseptal) emphysema:** Involves the distal part of the acinus. More severe in the upper half of the lungs. Possible cause for spontaneous pneumothorax in younger patients.
- **Compensatory emphysema:** Compensatory dilation of alveoli in response to loss of lung substance (loss of lung parenchyma after surgical removal).

Chronic Bronchitis

Persistent cough for at least three consecutive months in at least 2 consecutive years. Lacks eosinophils.

- **Mucus hypersecretion:** Feature of chronic bronchitis that begins in large airways. Irritants induce hypersecretion of mucous glands and cause hypertrophy of the glands.
- **Squamous metaplasia:** Develops in chronic bronchitis, followed by dysplastic changes in the lining epithelial cells (may lead to bronchogenic carcinoma).

Bronchiectasis

Permanent dilation of bronchi and bronchioles due to destruction of muscle and supporting tissues associated with chronic necrotizing infections. **Obstruction** and **chronic infection** contribute to the development of bronchiectasis.

- **Kartagener's syndrome:** Autosomal recessive disorder predisposing to bronchiectasis. There is a structural abnormality of the cilia impairing the mucociliary ladder. Associated with sterility in males.
- **Cystic fibrosis:** Widespread, severe bronchiectasis from obstruction and infection caused by the secretion of abnormally viscid mucus.

RESTRICTIVE LUNG DISEASE

Reduced expansion of lung parenchyma accompanied by decreased total lung capacity. FVC is reduced and the expiratory flow rate is normal or reduced proportionately. The FEV_1:FVC ratio is normal. Divided into two categories: **extrapulmonary** (due to obesity or Guillain–Barré syndrome) and **interstitial lung disease.**

Interstitial Lung Disease

Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS)

Microvascular endothelium and alveolar epithelium are damaged, leading to an inflammatory response dominated by neutrophils. Clinically causes a continuum of respiratory failure: acute-onset dyspnea, hypoxemia, bilateral pulmonary infiltrates, and finally to left-sided heart failure.

- **Honeycomb lung:** Pattern of diffuse interstitial fibrosis and dilated airspaces following the body's healing process after ARDS.

Idiopathic Pulmonary Fibrosis

Diffuse interstitial fibrosis of unknown etiology (possibly an immune response). Results in severe hypoxemia and cyanosis. Known causes (e.g., asbestos) must be ruled out.

Sarcoidosis

Multisystemic disease of unknown etiology characterized by noncaseating granulomas, predominately in the lung interstitium (has a lymphangitic distribution). Also typified by bilateral hilar adenopathy. Noncaseating granulomas are also seen outside the lungs.

- **Schaumann's bodies:** Laminated concretions composed of calcium and proteins found inside granulomas of sarcoidosis.
- **Asteroid body:** Stellate inclusions within giant cells found within the granulomas of sarcoidosis that characterize sarcoidosis.
- **Erythema nodosum:** Raised, red, tender nodules on the anterior aspects of the legs.
- **Lupus pernio:** Indurated plaques associated with violaceous discoloration in the region of the nose, cheeks, and lips.

Hypersensitivity Pneumonitis

An immunologically mediated response to an extrinsic antigen that involves type III and type IV hypersensitivity reactions affecting the alveoli.

Goodpasture's Syndrome

An uncommon disorder characterized by hemoptysis and glomerulonephritis secondary to anti-basement membrane antibody.

Wegener's Granulomatosis

Necrotizing vasculitis and parenchymal necrotizing granulomatous inflammation causing a clinical syndrome of hemoptysis, chronic sinus infections, and hematuria.

Caplan's Syndrome

An accelerated pneumoconiosis seen in patients with rheumatoid arthritis who are exposed to coal, silica, or asbestos.

VASCULAR LUNG DISEASE

Pulmonary Thromboembolism

Embolization of venous thrombi to the lungs. Most emboli arise from a deep venous thrombosis (commonly popliteal and more proximal veins).

- **Saddle embolus:** Large embolus that lodges across the bifurcation of the major vessels in the lung.

Pulmonary Hypertension

Increase in BP within the pulmonary vasculature. Primary pulmonary hypertension is caused by chronic vasoconstriction resulting from vascular hyperreactivity.

PNEUMONIA

Acute bacterial pneumonia presenting as one of two patterns: broncho-pneumonia and lobar pneumonia (hospital acquired, community acquired, and aspiration). Pathologically progresses through four stages: **congestion** (vascular congestion with fluid, neutrophils, and bacteria in the alveoli), **red hepatization** (alveoli are filled with neutrophils, red cells, and fibrin), **gray hepatization** (red cells are lysed and fibrinous exudates persist), and **resolution** (exudates within the alveoli are enzymatically digested and either resorbed or expectorated).

Bronchopneumonia

The distribution of inflammation that generally involves more than one lobe, and results from an initial infection of the bronchi and bronchioles with extension into the adjacent alveoli.

Lobar Pneumonia

The contiguous airspaces of part or all of a lobe are homogenously filled with exudates that can be visualized on radiographs as a lobar or segmental consolidation.

Community-Acquired Pneumonia

These are bacterial in origin and the infection usually follows a viral upper respiratory tract infection. The onset is usually abrupt, with high fever, shaking chills, pleuritic chest pain, and a productive mucopurulent cough. The lower lobe of the right lung is most commonly involved. The most common type of bacteria implicated in community-acquired pneumonia is *Streptococcus pneumoniae*. Numerous other bacteria can cause pneumonia. See Table 10-13.

Atypical Pneumonia

Sputum production is modest with no physical findings of consolidation, the white cell count is moderately elevated, and bacteria and influenza A viruses cannot be isolated. ***Mycoplasma pneumoniae*** and ***Chlamydia pneumoniae*** are frequent causes.

Nosocomial Pneumonia

Acquired in the course of a hospital stay. **Enterobacteriaceae** are the most common isolates in nosocomial pneumonias.

TABLE 10-13. Other Important Bacterial Causes of Pneumonia

BACTERIA	CHARACTERISTICS
Haemophilus influenzae	Community acquired. COPD exacerbations.
Moraxella catarrhalis	Community acquired. Also a common pathogen in otitis media in children.
Staphylococcus aureus	Frequently causes lung abscesses.
Klebsiella pneumoniae	Most frequent cause of gram-negative bacterial pneumonia. Afflicts debilitated and malnourished persons, particularly chronic alcoholics.
Pseudomonas aeruginosa	Common in patients afflicted with cystic fibrosis.
Legionella pneumophila	Associated with contaminated water sources (air conditioning units and vents).

Aspiration Pneumonia

Occurs in those who aspirate gastric contents while unconscious or during repeated vomiting. The pneumonia is due in part to chemical irritation and is partly bacterial. Complications include abscess formation.

TUBERCULOSIS

A communicable chronic granulomatous disease that involves the lungs, primarily caused by *Mycobacterium tuberculosis* (an acid-fast bacteria that readily bind the Ziehl-Neelsen stain). **Primary tuberculosis** develops in a previously unexposed person.

- **Ghon's focus:** Areas of gray-white inflammatory consolidation emerge typically in the upper lobes.
- **Ghon's complex:** Parenchymal lesion and nodal involvement.
- **Ranke's complex:** A Ghon complex that undergoes progressive fibrosis. Radiologically detectable calcification.
- **Tuberculin test:** Infection causes a delayed hypersensitivity reaction. Purified protein derivative (PPD) injected subcutaneously induces a palpable induration after 48–72 hours. False-negatives may occur with viral infections, sarcoidosis, or malnutrition.

Miliary Tuberculosis

Organisms drain from the lung via lymphatics to other parts of the lung, and then systemically.

- **Pott's disease:** Miliary spread of tuberculosis to the vertebrae.

Secondary (Reactivation) Tuberculosis

The pattern of disease arising in a previously sensitized host from reactivation of a dormant pulmonary lesion. Classically located in the apex of the lungs.

TABLE 10-14. Fungal Infection of the Lung

FUNGUS	CHARACTERISTICS
Cryptococcus neoformans	Cryptococcosis. Opportunistic infection seen in immunocompromised persons. The capsule is critical to diagnosis. Replicates through budding.
Aspergillus spp.	Opportunistic mold. Hyphae and septa branch at acute angles. In aspergilloma (fungus ball), the fungus may colonize preexisting pulmonary cavities.
Pneumocystis jiroveci (formerly *carinii*)	Opportunistic. Common infection in AIDS patients.

FUNGAL INFECTIONS

Several fungal infections can affect the lungs. Table 10-14 summarizes the more common types.

LUNG TUMORS

A presentation of hemoptysis and constitutional symptoms in a patient with risk factors (e.g., smoking history or asbestos exposure) should raise concerns for lung cancer. Chest X-ray may show a lung nodule. There are several types of lung cancer. Bronchogenic carcinoma arises from bronchial epithelium and accounts for 95% of lung tumors. Divided into small cell carcinoma and non-small-cell carcinoma (adenocarcinoma, squamous cell carcinoma, or large cell undifferentiated carcinoma).

- **Virchow's node:** Supraclavicular node signaling an occult primary tumor.
- **Vena cava syndrome:** Tumor compresses the superior vena cava, causing venous congestion or the full blown vena cava syndrome.
- **Pancoast's tumor:** Apical neoplasm that invades the brachial or cervical sympathetic plexus. Presents with pain in an ulnar nerve distribution, or Horner's syndrome (ipsilateral enophthalmos, ptosis, miosis, and anhidrosis).

Small Cell Lung Cancer

Appear as centrally located masses arising from neuroendocrine cells with extension into the lung parenchyma with early involvement of the hilar and mediastinal nodes. Clinically presents late in its course, making surgical treatment ineffective. Radiation and chemotherapy are the mainstays of treatment. Associated with several paraneoplastic syndromes.

- **Parathyroid hormone-related peptide:** Causes hypercalcemia.
- **Cushing's syndrome:** ACTH is secreted.
- **Syndrome of inappropriate secretion of ADH (SIADH):** A paraneoplastic syndrome associated with lung cancers.

Non–Small Cell Lung Cancer

Tumors are best treated with surgery, as they usually have not metastasized.

- **Adenocarcinoma:** Peripherally located lesions arising in relation to peripheral lung scars (scar carcinoma). Metastasize at an early stage.
- **Large cell carcinoma:** Group of neoplasms that likely are squamous cell or glandular neoplasms that are too undifferentiated to permit categorization. Tend to spread early in their development.

Bronchial Carcinoid

Arises from neuroendocrine cells that line the bronchial mucosa. Appear at an early age. Presents with findings related to intraluminal growth (cough, hemoptysis, and recurrent infection).

Malignant Mesothelioma

Rare cancer of mesothelial cells arising in the parietal or visceral pleura. Associated with occupational exposure to asbestos. The combination of cigarette smoking with asbestos exposure greatly increases the risk of malignant mesothelioma.

LESIONS OF THE UPPER RESPIRATORY TRACT

Infectious

Fever, sore throat, drooling, and difficulty breathing may be presenting symptoms. The age of the patient is also helpful in diagnosis. Physical exam may show a reddened oropharynx.

- **Pharyngitis:** Inflammation of the pharynx; manifests as a sore throat.
- **Epiglottitis:** Syndrome of young children with an infection of the epiglottis (*H. influenzae*) causing pain and airway obstruction.
- **Laryngitis/croup**

Benign Laryngeal Tumors

The most common clinical presentation is hoarseness.

- **Vocal cord nodules:** Smooth hemispheric protrusions located on the true vocal cords. These occur chiefly in heavy smokers and singers.
- **Laryngeal papilloma:** A benign neoplasm on the true vocal cords, that forms a soft, raspberry-like excrescence, and is rarely more than 1 cm in diameter.
- **Juvenile laryngeal papillomas:** Usually singular in adults but multiple in children. Associated with human papillomavirus types 6–11.

Carcinoma of the Larynx

Accounts for 2% of all cancers. Presents in patients aged > 40 years, more often in men than in women. Associated with smoking and alcohol consumption and asbestos exposure. Manifests as persistent hoarseness.

- **Glottic tumors:** On the vocal cords, usually keratinizing.
- **Supraglottic tumors:** Above the vocal cords; one-third metastasize.
- **Subglottic tumors:** Below the vocal cords.

Nasopharyngeal Carcinoma

Strong link to EBV. EBV infects the host by replicating in the nasopharyngeal epithelium and then infecting nearby tonsillar B lymphocytes. High frequency in the Chinese.

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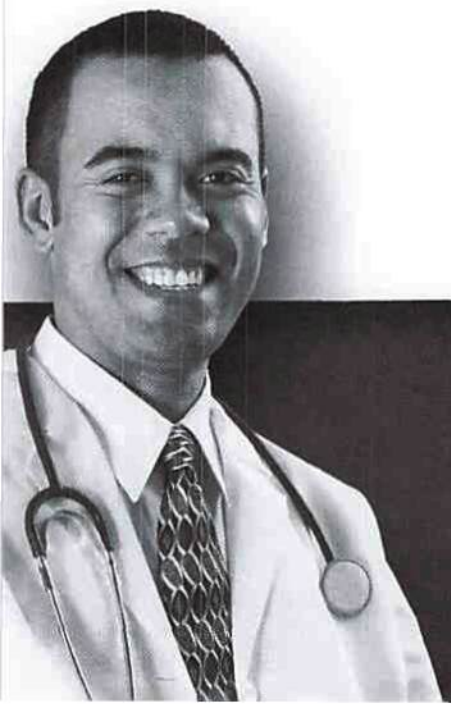
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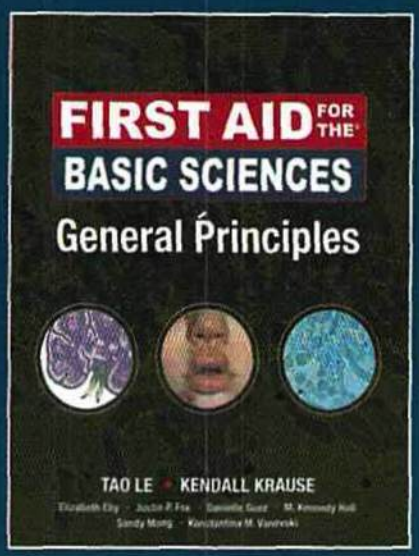
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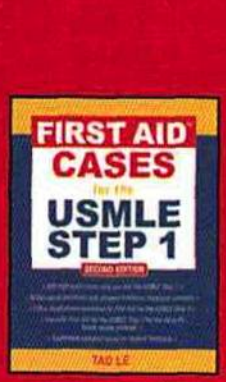
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